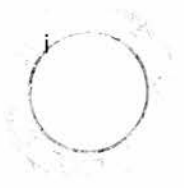


# The Utility of Out of Office Blood Pressure Measurement

Neil McGowan

Doctor of Medicine. The University of Edinburgh, 2010



<b>Contents</b>	ii
List of Tables	vi
List of Figures	viii
List of appendices	ix
Acknowledgements	x
Declaration	xi
Abstract	xii

**Chapter 1: Introduction**

The History of Blood Pressure Measurement	1
Hypertension and Office Blood Pressure	4
The Utility of Out of Office BP Measurement	7
Prognostic Significance of ABPM	12
Cost Effectiveness of ABPM	15
Self Blood Pressure Measurement	16
Prognostic ability of SBPM	18
How many measurements are needed?	19
Treatment and Out of Office BP Measurement	19
Blood Pressure Reproducibility	22
Conclusions	23
Outline of Thesis	24

## **Chapter 2: The Demographics of Hypertension and Reproducibility of Blood Pressure Measurement**

Background	28
Demographics of the untreated population	29
Reproducibility of blood pressure measurement	36
Discussion	39

## **Chapter 3: The Reproducibility of Nocturnal Dipping**

Background	45
Methods	46
Statistics	47
Results	47
Discussion	52

## **Chapter 4: The Use of Ambulatory Blood Pressure Monitoring in Primary Care**

Introduction	58
Methods	59
Statistics	61
Results	62
Discussion	68

## **Chapter 5: The Use of Ambulatory Blood Pressure Monitoring in Secondary Care**

Background	72
------------	----

Methods	74
Statistics	77
Results	77
Discussion	80

## **Chapter 6: How consistent are experts in reporting and interpreting ABPM?**

Background	87
Study 1: Therapeutic decision making based on ABPM within the cardiovascular risk clinic of the Western General Hospital	88
Study 2: Diagnosis and therapeutic decision making within members of the European Society for Hypertension Working Group on BP measurement	91
Study 3: Consistency of diagnosis and therapeutic decision making within members of the British Hypertension Society	93
Study 4: Expert versus computer based algorithm in ABPM diagnosis	95
Conclusion	103

## **Chapter 7: Self blood pressure monitoring: a worthy substitute for Ambulatory blood pressure**

Background	112
Methods	113
Statistics	115
Results	116



Discussion	118
------------	-----

<b>Chapter 8: Summary and Conclusion</b>	<b>122</b>
--	------------

Publications containing work undertaken for this thesis	129
---	-----

Oral presentations to learned societies containing work undertaken for this

Thesis	130
--------	-----

Bibliography	131
--------------	-----

<b>List of Tables</b>	<b>page</b>
Table 1.1      Summary of comparative studies detailing the difference between office blood pressure and daytime ambulatory blood pressure	<b>9</b>
Table 2.1      Mean ( $\pm$ SD) BP values of 5,167 patients on no antihypertensive treatment at time of first ABPM	<b>31</b>
Table 2.2      Blood pressure details for the 5,167 untreated patients with normal BP, White coat hypertension, masked and true hypertension	<b>33</b>
Table 2.3      Incidence of non-dipping in the untreated population as per blood pressure category (normal,WCH,masked or hypertensive), sex and age	<b>33</b>
Table 2.4      Mean office and ambulatory BP ( $\pm$ SD) & mean nocturnal dip ( $\pm$ SD) by age (decade) within the untreated population (n=5,167)	<b>34</b>
Table 2.5      Office and ABPM values in 284 patients before and after antihypertensive treatment was commenced	<b>36</b>
Table 2.6      Coefficient of variation (CV) derived from 512 treatment naive patients with two ABPM and 55 patients with three ABPM	<b>37</b>
Table 2.7      Kappa values for reproducibility of hypertensive/normotensive classification in 512 treatment naive subjects with 2 episodes of ABPM	<b>38</b>
Table 2.8      Intra-class correlation coefficients for both OBP and ABP in 512 treatment naive subjects	<b>38</b>

Table 2.9	Coefficient of Variation (CV) for OBP and ABP in 512 treatment naive subjects	<b>39</b>
Table 3.1	Baseline data of 512 subjects studied for reproducibility of nocturnal blood pressure fall	<b>47</b>
Table 3.2	Reproducibility of dipping with different time intervals between ABPM assessments	<b>49</b>
Table 3.3	The effect of varying sleep times on median percentage change in nocturnal BP dip	<b>51</b>
Table 4.1	OBP and ABP at time of diagnosis of hypertension in subjects subsequently treated or not treated	<b>63</b>
Table 4.2	Baseline ABP & OBP in monotherapy & dual therapy groups	<b>63</b>
Table 4.3	BP at diagnosis and one year post diagnosis for all patients, both pre nGMS and post nGMS contract	<b>67</b>
Table 5.1	Medications of study population (n=34) at entry and discharge from the cardiovascular risk clinic, and at six month follow up	<b>78</b>
Table 6.1	Who are assessed by ABPM prior to commencing therapy?	<b>93</b>
Table 6.2	Which value most influences your response?	<b>93</b>
Table 6.3	Which patients are assessed by ABPM during treatment?	<b>94</b>
Table 6.4	Which patients are assessed by SBPM?	<b>94</b>
Table 6.5	Summary results of questionnaire analysis	<b>100</b>
Table 6.6	Summary of dabl vs.expert interpretation	<b>101</b>
Table 7.1	Level of agreement between ABPM and SBPM for blood pressure when expressed as a continuous variable	<b>117</b>

<b>List of Figures</b>	<b>page</b>
Figure 2.1 Office and awake-time mean systolic pressure of 5,167 patients on no antihypertensive treatment at first assessment with ABPM	<b>30</b>
Figure 2.2 Office and awake-time mean diastolic pressure of 5,167 patients on no antihypertensive treatment at first assessment with ABPM	<b>31</b>
Figure 2.3 Bland Altman plot for systolic pressure in 512 patients with repeat ABPM	<b>37</b>
Figure 3.1 Distribution of percentage fall in nocturnal blood pressure in 512 patients with repeated ABPM assessments	<b>50</b>
Figure 3.2 Change in nocturnal fall between ABPM 1 and ABPM 2	<b>51</b>
Figure 5.1 Medication titration protocol for pharmacist led cardiovascular risk clinic	<b>85</b>
Figure 5.2 Summary of Results	<b>86</b>
Figure 6.1 Clinical Scenarios given to the members of the ESH working group on blood pressure measurement – Does ABPM help and how?	<b>92</b>
Figure 6.2 Example pages from Spacelabs report	<b>98</b>
Figure 6.3 Extract from the corresponding 1-page dabl report	<b>99</b>
Figure 7.1 Bland Altman plot of systolic pressure comparing SBPM with ABPM	<b>118</b>

**List of appendices**

Appendix 2.1 Sample ABPM report **44**

Appendix 6.1 Clinical Decision-making using Ambulatory Blood Pressure Monitoring (ABPM) and Self (Home) Blood Pressure Monitoring (SBPM) **107**

Appendix 6.2 Expert participants from the dabl®Educational Trust Advisory Board **111**

## Acknowledgements

I am greatly indebted to Professor Paul Padfield who has supervised and mentored me throughout. Without his advice and guidance this project would have foundered long ago.

Many thanks to Sister Kathleen Gough who advised on many aspects of the studies contained within. In addition, thanks to all of the nursing staff of the metabolic unit in the Western General who helped with the day-to-day running of the clinical projects.

Thanks to Dr. David Cunningham (Central cardiac audit database) for his help with the regression analysis in chapter 2 and Geoff Cohen (statistician) for his help with intra-class correlation coefficients in chapter 7

Lastly, many thanks to my wife for her continuing support.

## **Declaration**

The work contained within this thesis was carried out whilst I was employed as an endocrine registrar in Edinburgh. The work contained within and the writing of this thesis was entirely my own work. As a body of work, it has not been submitted for any other qualification. Publications derived from this work are clearly stated.

## Abstract

Ambulatory blood pressure measurement (ABPM) has improved prognostic power with respect to cardiovascular disease compared with office blood pressure (BP). It can be postulated that this is secondary to improved reproducibility of measurement, as a result of ABPMs ability to remove most of the factors leading to within-subject variability of BP measurement. In addition, the number of BP readings obtained from ABPM results in a statistically more accurate reflection of mean BP compared with a single office BP measurement.

Repeated episodes of ABPM, with time intervals of six months to greater than three years, were examined in a cohort of treatment naïve subjects. BP was more reproducible when expressed as a continuous variable, as defined by the intra-class correlation coefficient (ICC), than when BP was referred to as a dichotomous variable (hypertensive / normotensive), as defined with a kappa statistic. This was true independent of time interval between episodes of monitoring.

Linear regression analysis or multivariate binomial regression indicated that nocturnal blood pressure dip, expressed as either a continuous or dichotomous variable, was unable to be predicted from age, sex, mean awake systolic BP.

Nocturnal blood pressure dipping was poorly reproducible when expressed as a dichotomous variable (dipper/non-dipper), irrespective of the time interval between measurements ( $\kappa=0.29$ ). Intra class correlation coefficient demonstrated improved reproducibility of nocturnal pressure fall when this is expressed as a percentage reduction of mean awake BP (ICC=0.6). This was constant independent of time interval. ABPM was used to demonstrate a significant BP reduction in patients with diabetes and high vascular risk, managed through a pharmacist-led cardiovascular risk clinic. Repeat ABPM six months post discharge was not significantly different from BP on discharge from the clinic.

ABPM data currently needs clinician interpretation. Four studies, using national and international experts in hypertension, indicated poor agreement in interpretation and diagnosis of hypertension when all were faced with identical ABPM data. Computer software can be used to standardise diagnosis but management decisions will always rest with clinicians.

Self blood pressure monitoring has been proposed as the future of hypertension management. Mean BP obtained with self monitoring of BP (SBPM), using the schedule defined by the European Society of Hypertension, was not significantly different to mean awake-time BP on ABPM. In addition, SBPM was preferred by over 80% of subjects.

The author suggests that using only office BP for measuring blood pressure is outdated and inaccurate. The aim of this thesis was to demonstrate the utility of out of office blood pressure measurement and recommends this becomes part of everyday clinical practice.

It is time hypertension management was brought into the 21<sup>st</sup> century!



## Chapter 1

### ***The History of Blood Pressure Measurement***

Blood pressure measurement and its therapeutic manipulation are ubiquitous in the field of medicine. However, blood pressure measurement as we know it today has taken many centuries of refinement, with respect to not only our understanding of the physiology, but also the technical advances needed for accurate measurement.

Over 100 years passed between discovery of the circulation by William Harvey (1628) and the demonstration of the pressures within this circulation by Reverend Stephen Hales, *"having laid open the left crural artery....I fixed a glass tube, which was 9 feet in length: then untying the ligature on the artery, the blood rose 8 feet 3 inches perpendicular above the level of the left ventricle of the heart"* (Hales, 1733). A further hundred years was to pass before this was applied to human physiology, presumably as not many humans were keen on glass tubes being inserted into their femoral arteries. In 1828, Poiseuille was the first to develop a mercury sphygmomanometer to measure intra-arterial blood pressure but it was Faivre who used this, during a limb amputation, to measure systolic arterial pressure in man for the first time.

In 1833, Jules Harrison invented a mercury reservoir covered with a rubber membrane, linked to a glass tube to allow estimation of systolic blood pressure, thereby allowing indirect measurement of blood pressure. This was further refined by Marey but his device was inaccurate at recording pressure and he was more interested in the arterial waveform. All of the first sphygmographs worked on the same principal – a screw

applied to the radial artery was able to trace the pulse and by applying weights to the device, a pressure could be measured. The same principal resulted in a common problem – blood *pressure* was not be accurately assessed as pressure was being applied to the whole artery rather than taking into account the arterial surface being compressed (Janeway 1904).

The term “sphygmomanometer” was coined by Siegfried Ritter von Basch in 1880. Using rubber tubes connected to cadaveric arteries, he demonstrated the pressure required to occlude the artery was equal to the intra-arterial pressure plus the pressure required to overcome the vessel wall rigidity. As the latter is negligible, occlusion pressure approximates systolic arterial blood pressure.

The next steps, made by Riva-Rocci and Korotkov circa 1900, were to change blood pressure measurement into how we know it today. Riva-Rocci developed the inflatable bladder within leather that encircled the upper arm. Inflation of the bladder by a pump sufficient to occlude the distal pulse was measured by a mercury sphygmomanometer. Heinrich von Recklinghausen suggested the bladder cuff size was of critical importance to achieve accuracy of measurement and not falsely high readings. Nicolai Korotkov, a Russian surgeon, was the first to describe the auscultatory method of blood pressure measurement, in a paper delivered to the Imperial Military Academy in St.Petersburg in April 1905:

*“The cuff of the Riva-Rocci is placed on the middle third of the upper arm; the pressure within the cuff is quickly raised up to complete cessation of the circulation below the cuff. Then, letting the mercury of the manometer fall, one listens to the artery just below*

*the cuff with a children's stethoscope. At first no sounds are heard. With the falling of the mercury in the manometer down to a certain height, the first short tones appear; their appearance indicates the passage of part of the pulse wave under the cuff. It follows that the manometric figure at which the first tone appears corresponds to the maximal pressure. With the further fall of the mercury in the manometer one hears the systolic compression murmurs, which pass again into tones (second). Finally, all sounds disappear. The time of cessation of sounds indicates the free passage of the pulse wave; in other words, at the moment of the disappearance of the sounds the minimal blood pressure within the artery predominates over the pressure in the cuff. It follows that the manometric figures at this time correspond to the minimal pressure."*

After more than 100 years, this remains the cornerstone of blood pressure measurement.

Whilst this is still the most widely used method of measurement, conventional indirect measurement of blood pressure is prone to a variety of errors. Cuff size, observer prejudice, terminal digit preference (Burnier et al 2008) and confusion over which Korotkov sound signifies diastolic pressure (phase IV or V) all lead to significant error (O'Brien et al 2003). Both the London School of Hygiene and random zero sphygmomanometer were introduced to diminish observer prejudice and terminal digit preference but both of these have now been abandoned due to different sets of inaccuracies. Recognition of these problems, along-with the desire to assess blood pressure at different times of day (including nocturnal pressure), has led to the development of automated blood pressure measurement.

### ***Automated non-invasive blood pressure measurement***

The first automated non-invasive device was developed in 1921 by Blankerhorn, mainly due to his interest in the effect of sleep on blood pressure, a theme to which I will return. It took approximately 40 years before this was developed and in 1962 Hinman described the first case of a portable non-invasive ambulatory blood pressure recorder. This device required the wearer to activate the cuff inflation and therefore readings were limited to day-time (Hinman et al 1962). Although this had its limitations, it allowed Perloff and Sokolow (Perloff et al 1983) to demonstrate for the first time that “out of office” blood pressure readings were better predictors of morbidity and mortality than office blood pressure. Over the last thirty years, a variety of companies (Del Mar Avionics, Spacelabs, Microlife etc) have further refined these non-invasive blood pressure meters, moving from microphone/auscultatory methods to oscillometric, such that 24-hour ambulatory, and self blood pressure meters, are commonplace in clinical medicine.

Validation of ambulatory and self-measurement devices was originally carried out according to the British Hypertension Society (O'Brien et al 1990) and the Association for the Advancement of Medical Instrumentation (AAMI, 1987) protocols and, more recently, the International Protocol (O'Brien et al 2002).

### ***Hypertension and Office Blood Pressure***

Hypertension has been variably defined over the years but current guidelines define an office blood pressure (OBP) of  $> 140/90\text{mmHg}$  as hypertension (JNC VI 1994, WHO 1999, Williams et al 2004). It is estimated to affect more than half of the American population over 65 years of age (Pickering et al 2005) and is one of the most important

modifiable risk factors for the development of cardiovascular disease. There is a continuous positive linear relationship between it and development of cardiovascular disease. An increase of 10 mmHg systolic or 5mmHg diastolic is associated with a 40% increase in stroke death and 30% increase in death from ischaemic heart disease, at least with systolic pressures above 115mmHg (Lewington et al 2002). Numerous clinical trials have demonstrated that treating hypertension reduces cardiovascular morbidity and mortality. However, the blood pressure measurement most commonly used in these trials is “office” blood pressure. Apart from the measurement inaccuracies documented already, repeated measurement of blood pressure, in the absence of any therapeutic intervention, will lead to a change in measured blood pressure, a phenomenon entitled “regression to the mean”. This was best exemplified by the MRC trial of mild hypertension where blood pressure fell by 10/6 mmHg within the first month in the placebo arm of the trial (MRC 1985). To clarify the terminology, “habituation” is essentially the same as regression to the mean for the purposes of hypertension clinical trials. Entry to these trials use hypertension as a screening tool, thereby ruling out patients whose blood pressure will rise with time. True regression to the mean would include all subjects, some of whom would be hypertensive and some with lower blood pressure. Repeated measurement would mean that some would have a fall in blood pressure but also some would have a rise in blood pressure, both regressing to their own mean BP.

Blood pressure variability, expressed as either standard deviation in relation to the mean, or coefficient of variation, occurs as a result of patient factors, observer factors, the interaction between patient and observer, and the measurement device used. Many

patient factors affect each measurement thereby leading to increased variability e.g. timing of concurrent medication, sitting with legs crossed, a full bladder, recent ingestion of caffeine or nicotine etc. In an effort to minimize the contribution of each of these factors, very clear guidance has been published on routine office blood pressure measurement (Pickering et al 2005). In addition, as age and blood pressure increase, so does the variability of measurement, probably as a result of abnormal baroreceptor reflex and increased arterial stiffness (Imai et al 1997).

As mentioned above, conventional sphygmomanometry allows different forms of observer error, such as rounding errors, terminal digit preference, inappropriate cuff size and identification of phase IV or V Korotkoff sounds. A substantial amount of variation is introduced as a result of patient / observer interaction. The abnormal elevation of BP in a medical setting ('white coat hypertension' in a true normotensive patient or 'white coat effect' in a known hypertensive), probably due to a transient increase in sympathetic nervous system activity, is perhaps the most well recognised problem leading to within-patient variation. This is present whether the observer is a nurse or physician, albeit a more exaggerated response with physician measured BP (Little et al 2002).

With respect to the measurement device used, factors including concern over mercury have led to poor maintenance of traditional sphygmomanometers. As a result, most are not as accurate as they once were. Increasing use of validated oscillometric devices should minimize observer error and device-error, with resultant improvements in reproducibility (Myers et al 2009).

Considering all of the above problems with blood pressure variability and office blood pressure measurement, it has been postulated that “out of office” blood pressure measurement (both ambulatory and self-blood pressure measurement) is the best way forward for the diagnosis and on-going management of hypertension (Pickering 1996, 2008, Padfield 2002, O’Brien 2003).

### ***The Utility of Out of Office BP Measurement***

Ambulatory blood pressure measurement (ABPM) can be thought of as the gold standard in blood pressure measurement for several reasons. It is superior to office blood pressure alone in determining prognosis (Pickering et al 2006), more reproducible than office BP (James et al 1988), recommended in diagnosing white coat hypertension and masked hypertension (O’Brien et al 2005) and gives information on nocturnal pressure, itself an indicator of prognosis in terms of cardiovascular disease (O’Brien et al 1988, Boggia et al 2007).

The definition of hypertension based on OBP has already been discussed and represents the dichotomisation of a continuum within the population. When out of office blood pressure (i.e. ABPM or SBPM) is measured, another level of complexity is added and more definitions are taken into account. ‘True’ hypertension is hypertension on office and out of office BP and normotension is obviously normal BP using both methods. White coat hypertension is hypertension on office measurement but normal on out of office measurement and masked hypertension is the reverse i.e. normal office BP and hypertensive out of office BP. If office BP is ignored and only out of office measurements are used, we are back to hypertensive or normal, albeit still either side of an arbitrary line.



Much has been written on how daytime BP, measured using ambulatory devices, equates to office measured BP, with corresponding values derived from different studies. Using regression analysis, the PAMELA study equated an office BP of 140/90mmHg with a daytime ABPM pressure of 130/85mmHg (Mancia et al 1995). However, the relationship between OBP and daytime ABP is complex, with differences dependent on age, sex and presence or absence of hypertension. Most recently, Head et al analysed ABPM data on over 8500 patients. Their data suggested not only is the difference between OBP and ABP dependent on who (nurse or physician) takes the OBP but the difference also increases as the severity of hypertension increases (Head et al 2010). Table 1.1 summarises studies which have explored the difference between OBP and daytime BP on ABPM.

The data presented in chapter 2 clearly shows not only blood pressure rising with age, but the difference between OBP and daytime ABP also increases progressively with age. In 2004, the BHS suggested the mean daytime BP on ABPM should be estimated to be 10/5mmHg lower than contemporaneous OBP (Williams et al 2004), presumably as it was too complex to include all the variables which influence the outlined differences. To simplify matters, I have used the difference quoted by the BHS (10/5mmHg) throughout this thesis.



Table 1.1. Summary of comparative studies detailing the difference between office blood pressure and daytime ambulatory blood pressure (all pressures in mmHg)

Study	Population / variable	Office BP	ABPM	Difference
Head et al (2010)	Doctor measured (n=1593)	150/89	136/80	<b>14/9</b>
	Nurse measured (n=8529)	142/82	136/79	<b>6/2</b>
Blanco et al (2006)	Normotensive (n=68)	123/72	121/72	<b>2/0</b>
	Hypertensive n=(224)	157/88	135/78	<b>22/10</b>
Little et al (2002)	Doctor measured (n=179)	ns	ns	<b>19/11</b>
	Nurse measured (n=194)	ns	ns	<b>9/10</b>
Hozowa et al (2002)	Normotensive (n=625)	121/70	124/74	<b>-3/-4</b>
	Hypertensive (n=150)	154/84	136/80	<b>18/4</b>
Bjorklund et al (2000)	Males age 70 (n=1060)	140/90	137/83	<b>3/7</b>
Staessen et al (1999)	Age>60, n=808	173/86	151/84	<b>22/2</b>
Schettini et al (1999)	Untreated patients, n=1573	140/90	129/84	<b>11/6</b>
Rasmussen et al (1998)	Male (n=959)	130/83	137/79	<b>-7/4</b>
	Female (n=859)	125/80	128/79	<b>-3/1</b>
Verdecchia et al (1994)	Normotensive (n=205)	126/79	123/79	<b>3/0</b>
	Hypertensive (n=693)	159/98	145/93	<b>14/5</b>

Key: ns-not stated

Until recently, hypertension on ABPM or SBPM was defined as daytime mean blood pressure of >135/85 mmHg (Williams et al 2004). This was derived using reference data from the normal population with hypertension defined as a blood pressure above the 95<sup>th</sup> centile (Mancia et al 1995, Sega et al 1997). However, perhaps as a result of outcome data relying on office measurements from clinical trials, there is lack of

consistency amongst hypertension specialists in how ABPM is reported and interpreted (McGowan et al 2007). Recently, the diagnostic thresholds for ABPM have been re-drawn based on cardiovascular outcome data from over 5,000 people. It defined optimal awake blood pressure as  $< 120/80$  mmHg, normal  $< 130/85$  mmHg and hypertension as  $>140/85$  mmHg (Kikuya et al 2007). However, accepting the average 10/5mmHg difference between ABPM and office BP, does this mean office BP diagnosis should change to  $> 150/90$ mmHg?

Due to the problems of white coat hypertension and masked hypertension, it can be seen that using only office blood pressure is problematic. Both will be wrongly categorised or not even found and therefore, managed inappropriately. This is not an insignificant problem. Population studies have demonstrated rates of white coat hypertension and masked hypertension of 9-13% and 9-17% respectively (Sega et al 2001, Ohkubo et al 2005, Stergiou et al 2005) but long term follow up studies have differed slightly in terms of relative risk of cardiovascular disease attributable to masked hypertension and white coat hypertension. Sega et al demonstrated an increase in left ventricular mass in both white coat and masked hypertension, to an equal extent, when compared to normotensive subjects in the PAMELA study (Sega et al 2001). The Framingham Heart Study demonstrated a direct correlation between left ventricular mass and cardiovascular morbidity and mortality (Levy et al 1990) therefore the implication is that both masked hypertension and white coat hypertension are associated with increased cardiovascular risk. However, whilst Mancia et al found white coat hypertension and masked hypertension to have a hazard ratio of 2 for cardiovascular death when compared to true normotension (Mancia et al 2006), Ohkubo

et al found only masked hypertension, not white coat hypertension, had an increased risk cardiovascular and stroke death (relative risk 2.13) in the Ohasama population (Ohkubo et al 2005).

Out of office blood pressure measurement, both ABPM and SBPM, can be used to identify these problems. However, the proposed differences between OBP and ABPM or SBPM are not 100% clear. In terms of mean awake ABP, I have already discussed the 10/5mmHg difference compared to OBP. The difference between SBPM and OBP is not as clear. The British Hypertension Society (BHS) estimated the difference to be the same as with ABPM (Williams et al 2004) but other studies have found this to vary from 7/5mmHg (Verberk et al 2005) to 15/6 mmHg (Little et al 2002). It seems both of the latter studies are variation around the mean difference as quoted by the BHS as most studies directly comparing ABP with SBP have found no difference between mean awake ABP and mean SBP (Stergiou et al 2000, Cesar et al 2003, Carney et al 2005). Chapter 7 deals with this in some detail.

Diagnosing hypertension based on SBPM, ABPM or office BP has been investigated by Stergiou (2000) and Jula (1999). As in the MRC trial, both found regression of office blood pressures. Stergiou used 2 episodes of ABPM, 5 days of SBPM and 5 office visits. Although this may have represented “real life”, the obvious flaw is difference between the number of blood pressure readings. As discussed below, more measurements invariably give a more accurate result. However, there was no difference between SBPM and ABPM in terms of diagnosis of hypertension although 6% more were diagnosed with hypertension using out of office measurements than office measurements, implying masked hypertension. Jula found SBPM and ABPM were

equivalent in terms of predicting target organ damage. Unusually, there was no significant difference between office BP and out of office measurements but this was probably due to the very controlled environment in which the office pressure was checked during this study (15 minutes rest, 5 minutes with BP cuff on prior to inflation, average of 4 BP measurements).

### ***Prognostic significance of ABPM***

Perloff and Sokolow were the first to demonstrate the improved prognostic value of ABPM over office BP in the hypertensive population. The ABPM device was patient activated therefore only daytime readings were obtained. In a cohort of over 1000 patients, daytime ABPM was superior to office BP in predicting fatal and non-fatal cardiovascular events, although only in those with no prior cardiovascular events (Perloff et al 1983). The Syst-Eur trial (untreated systolic hypertensive patients) and the Dublin Outcome study (untreated hypertension) found no difference in cardiovascular mortality between highest and lowest office blood pressures but an increased risk of cardiovascular and stroke death of 21 to 34% per 10 mmHg increase in nocturnal blood pressure. This increase in risk was substantially more than the risk (12%) associated with each 10mmHg increase in daytime BP (Staessen et al 1999, Dolan et al 2005). Many specialists within the field now agree that nocturnal pressure is the best for predicting cardiovascular risk and it is worth considering why this is the case. It is easy to see why BP is variable during the day-constant postural changes, varying autonomic outflow etc. therefore it will be difficult to get an accurate reflection of true mean BP by any method of measurement. There are far fewer external stimuli during sleep, making

nocturnal BP a more stable and accurate reflection of true BP. This is evidenced by the differences in coefficient of variation in the Syst-Eur trial (Staessen et al 1999). However, this is not the case with my data presented in chapter 2.

The independent prognostic power of ABPM in patients with treated hypertension has also been demonstrated. Relative risk of fatal or non-fatal cardiovascular events is increased by 30% for a 1 standard deviation increment in daytime systolic pressure (similar values for diastolic and night-time pressure changes) even after adjustment for all other risk factors and office BP. The relative risk increased to 56% per standard deviation when “cardiovascular events” was refined to fatal or non-fatal myocardial infarction or stroke (Clement 2003). Unusually, daytime, rather than nighttime, blood pressure demonstrated improved prognostic power for MI or stroke (RR daytime 1.56, nighttime 1.25) in this cohort of treated hypertensive patients. This may have been confounded by antihypertensive therapy, which tends to be given in the morning, and will adjust principally the daytime, rather than nocturnal blood pressure. Also, the number of events in this group was small, compared to the total cardiovascular events.

However, the majority of evidence supporting the prognostic value of ABPM has come from two large population based studies, the Pressioni Arteriose Monitorate e Loro Associazioni (PAMELA) study from Monza, Italy and the Ohasama study, Japan.

The PAMELA study enrolled 2054 subjects between age 25 & 74 to represent the general population. Office BP, SBPM and ABPM was carried out on each subject. Follow up was on average 11 years but only fatal cardiovascular and non-cardiovascular events were documented. Essentially, whilst office BP was equal to

SBPM and ABPM in predicting death, the risk increased more with a given rise in out of office blood pressure than office blood pressure. Once more, nocturnal blood pressure was superior to daytime pressure in predicting cardiovascular death, a value only obtainable with ABPM (Sega et al 2005).

The Ohasama study in Japan recruited 1332 subjects, representative of the general population. Office BP and ABPM was carried out on all subjects. The most recent follow up data is at 10.8 years. Interestingly, on reporting the findings, any deaths within the first 2 years were excluded from analysis to remove the possibility of reverse causality i.e. those patients with low blood pressure at inclusion may have had severe concomitant disease and therefore more likely to die. Although there was a relatively low incidence of cardiovascular deaths (5% of the study population), the relative risk of cardiovascular mortality was increased by 45% per 10mmHg rise in 24-hour blood pressure but only 6% per 10mmHg rise in office BP, which confirmed the improved prognostic ability of ABPM over office measurement. When night and day BP were compared, night-time BP was significantly better at predicting cardiovascular and stroke death, RR 1.32 vs. 1.03 (Kikuya et al 2005).

Most recently, Boggia et al have reported on behalf of the International Database on Ambulatory blood pressure monitoring in relation to Cardiovascular Outcomes (IDACO). Office and ambulatory measurements were carried out on 7,458 subjects, principally general population although 22% were being treated for hypertension, with a mean follow up of 9.6 years. Subsequent meta-analysis aimed to determine the prognostic accuracy of day versus night blood pressure. In terms of fatal endpoints, night-time pressure was superior to day time pressure. The night/day ratio was of prognostic use

in patients when determining total cardiovascular and non-cardiovascular mortality although this accuracy was lost when non-fatal events were included in the analysis (Boggia et al 2007). These findings challenged the previously held belief that nocturnal blood pressure has the greatest prognostic accuracy as it only appeared to be useful in terms of fatal endpoints. The biggest confounder that could not be adjusted for was antihypertensive therapy. Most blood pressure drugs are given in the morning therefore affect daytime pressure but night-time pressure may be affected to a lesser degree therefore in those on treatment, the ratio of night to day will be smaller. This is addressed in chapters 2 & 3.

All of these studies, whether population based, untreated or treated hypertension, have confirmed the improved prognostic ability of ABPM over office BP.

### ***Cost Effectiveness of ABPM***

ABPM has been approved for reimbursement by Medicare in the US for the diagnosis of hypertension and used predominately in the UK by secondary care organisations, funded through the NHS therefore it is worth briefly examining the arguments for the cost effectiveness of ABPM.

Cost effective analysis is complex and needs to take into account the incidence of hypertension, the prevalence of white coat hypertension (and what proportion will then develop hypertension), the cost of ABPM itself and the cost of treatment (including medication, visits to the doctor, blood tests). The main determinants of cost are the annual incidence of hypertension (and therefore drug costs) and the treatment strategy employed. The savings from using ABPM as a screening tool arise from the



identification of white coat hypertension. The authors of cost benefit analyses (e.g. Krakoff 2006) suggest those with WCH do not necessarily require treatment and this is where savings are made. However, this could be debated as Mancia et al demonstrated an increase in cardiovascular risk in those with white coat hypertension compared with normotension, although not as high as hypertension (Mancia et al 2006).

It appears to be cost effective when used as a secondary screening tool within the general population i.e. after hypertension is found by routine screening in primary care, ABPM has been used to distinguish between true hypertension and white coat hypertension. Used in this way, it is estimated to save at least \$334 per patient per year (Krakoff 2006).

Cost effectiveness of ABPM in determining adequate treatment of known hypertensives has been examined by Lorgelly et al (2003). The net cost of annual ABPM on a treated hypertensive primary care population of 374 patients was £3,612 i.e. just under £10 per patient. It is worth pointing out that this analysis was done prior to the implementation of the new General Medical Services contract and therefore this cost may rise if the 31% of this study population who achieved blood pressure control on ABPM but not office BP were claimed as 'controlled' for the BP5 section of the contract.

### ***Self Blood Pressure measurement***

There was less evidence regarding SBPM when compared to ABPM but this has changed. SBPM has 3 main purposes: (1) the diagnosis of hypertension; (2) accurate



titration of antihypertensive medication;(3) long term monitoring of BP control in known hypertensives.

The main advantages of SBPM over OBP are to allow multiple measurements of blood pressure therefore an improved estimation of true blood pressure. This will include regression to the mean blood pressure and possibly a lower blood pressure without any pharmacological treatment. It allows identification of white coat hypertension and masked hypertension (O'Brien et al 2005), both equally important as neither are without cardiovascular risk (Ohkubo et al 2005). The main disadvantage is lack of reference range for normality in the general population.

With respect to SBPM, several points need to be addressed: How does it compare to office measurement and ABPM; does it have prognostic value; does it improve blood pressure control; is it cost effective and how reliable are the self reported measurements?

SBPM and ABPM have been compared directly on the same day and same patient, with patients excluded who had a >10 mmHg systolic or > 5mmHg diastolic difference between arms at screening measurement. There is no difference between mean day BP and SBPM average in either normotensives, treated or untreated hypertensives (Carney et al 2005). Little (2002) and Cesar (2003) found similar equality with ABPM and SBPM although this is not always the case (Sega et al 1997, Stergiou 2000).

Whilst there appears to be numerical equality between mean ABPM and SBPM, this does not always translate into equality in terms of diagnostic category i.e. hypertension, masked hypertension, white coat hypertension and normotension. Stergiou and

colleagues have examined this in some detail. In both treated and untreated hypertensive subjects, SBPM and ABPM correlated highly ( $r = 0.7$ ) in detecting white coat effect (Stergiou et al 2004). Equal proportions of treated and untreated hypertensives have white coat hypertension or masked hypertension (12%) when SBPM is compared with ABPM, although these were not always the same 12% (Stergiou et al 2005). I have further investigated this in chapter 7. In terms of predicting target organ damage in hypertension, as defined by left ventricular mass and microalbuminuria, self-monitoring is as reliable as ABPM, with both superior to office measurement (Stergiou et al 2007, Gaborieau et al 2008).

### ***Prognostic ability of SBPM***

Three population based studies and one study of treated hypertensive patients have examined the prognostic significance of SBPM. Ohkubo and colleagues have reported 10-year follow up data on SBPM from the Ohasama trial. Each 10mmHg rise in SBPM increased the risk of stroke by 29%. This relationship was significantly better than with OBP (Ohkubo et al 2004a). Whilst the PAMELA trial found ABPM, SBPM and OBP all predicted CVD mortality, with the strongest relationship existing with SBPM (Mancia et al 2006), the Didima study demonstrated both SBPM and OBP predicted cardiovascular mortality although neither superior (Stergiou et al 2007). Only the SHEAF study has examined prognostic abilities of SBPM in treated hypertensives. After controlling for age, smoking status and previous cardiovascular disease, OBP was not predictive of CVD events but SBPM demonstrated a 17% increase in CVD events for each 10mmHg increase in systolic pressure. Interestingly, they also found CVD event hazard ratios of 2.06 for masked hypertension (i.e. BP control on OBP but not on SBPM) and 1.18 for

white coat hypertension, clearly demonstrating that OBP alone is insufficient in the follow up of treated hypertensive patients (Bobrie et al 2004).

### ***How many measurements are needed?***

Clinical studies to date have used widely ranging different numbers of self-measurements. In the studies mentioned above, PAMELA used 2 measurements, Didima used 12 and SHEAF used 28. Most information can be gleaned from the Ohasama study. They used a variety of numbers of home measurements, from one to 28, and examined the predictive nature of SBPM. Even one home measurement was better than OBP for predicting stroke but the strength of this prediction increased with increasing number of measurements (Ohkubo et al 2004b). Considerable opinion exists within the published literature (Stergiou et al 1998, Den Hond et al 2003, Ohkubo et al 2004, Verberk et al 2006, Padfield et al 2007, Imai et al 2007) regarding the number of home measurements needed however the current recommendations from the ESH and AHA are that a minimum of 24 self measurements are needed for clinical decision making (Parati et al 2008, Pickering et al 2008).

### ***Treatment and out of office BP measurement***

Antihypertensive drug adjustment based on SBPM, ABPM or office BP has been investigated. Staessen conducted a randomized controlled trial to examine whether BP control was different when treatment decision were made using ABPM versus office BP measurements. Similar levels of blood pressure control were achieved in both groups but the ABPM group was on significantly less medication. However, in this trial, diastolic pressure was used to adjust medications, not taking into account the differences

between ABP and OBP (Staessen et al 1997). Niiranen compared SBPM and ABPM in a similar fashion with no significant difference between ABPM and SBPM demonstrated in terms of numbers of patients achieving BP control (Niiranen et al 2006).

The position of SBPM as a guide to adjustment of antihypertensive medication is not clear. Initial investigation by Rogers et al demonstrated a significant 5/2mmHg reduction in BP in the study group allocated to SBPM with the responsible clinician sent a copy of BP reports by telemetry on a weekly basis then adjusting therapy. However, in both the control and intervention group, BP dropped. Also, BP fell in the section of the intervention group with no alteration in medication (Rogers et al 2001). Therefore, it was not clear whether the reduction in BP was regression, improved compliance to existing medications or a real treatment effect. The use of telemetry in this study circumvented subject-reporting bias as precision of reporting of SBPM has been shown to be approximately 75% (Mengden et al 1998).

More recently, Green and colleagues have further explored the benefits of SBPM over a 12-month period using Web-based communication (Green et al 2008). Subjects with uncontrolled hypertension were assigned to either usual care, SBPM with Web-based, patient-initiated communication with their doctor or Web-based communication with their doctor and specialist pharmacist, initiated by either subject or pharmacist. In terms of subjects achieving <140/90mmHg compared to usual care, the group assigned to patient initiated Web based communication with their doctor had a non-significant improvement of 5% and the subjects in the “intensive” last group had a 25% improvement, possibly due to the increased antihypertensive prescription in this group. This was not surprising as they were more intensively looked after, with the vast

majority of Web communication being initiated by the pharmacist (18 messages) rather than the subjects (4.2 messages). However, patient initiated messages were significantly greater compared to the Web system without the pharmacist implying a greater input from the pharmacist led to increased subject interest and self-management. What still remains unclear is how much the mean change in blood pressure in the intensive group (-14/7mmHg) can be attributed to the mean increase in medication prescription (0.5 antihypertensive drug class) and how much was attributable to simply monitoring the blood pressure more frequently thereby allowing pressures to regress to the mean and improve compliance with existing medication. In contrast, the THOP trial suggested blood pressure was less well controlled when home blood pressures were used to titrate antihypertensive medications although no difference in end organ damage was demonstrable (Den Hond et al 2004). Recent reviews (Cappuccio 2004, Fahey 2007) and the study by Halme (Halme et al 2005) have suggested SBPM has a small benefit in the management of hypertension with a reduction in BP of 2.2-3.5/1.9 mmHg (Cappuccio 2004, Halme 2005). Whilst this is a small reduction, it has the potential to be of significance if applied across the hypertensive population as a whole.

### ***Blood Pressure Reproducibility***

Blood pressure is naturally variable and therefore will not be 100% reproducible. Confidence in an accurate diagnosis or treatment effect relies on the assumption that measured blood pressure accurately reflects the true mean pressure i.e. the repeated measures have not simply occurred by chance. The gold standard of blood pressure measurement to achieve a true mean blood pressure would be invasive 24 hour arterial monitoring. The other end of the spectrum is single BP measurements in a clinical setting. Neither of these is ideal. ABPM or SBPM are a compromise between the two extremes. Multiple measurements of blood pressure will lead to a statistically more accurate estimation of the true pressure. It therefore follows that ABPM or SBPM will be more reproducible than office BP, simply by having more measurements. This could explain why the SAMPLE study, which evaluated the effect on LV mass after one year of treatment with lisinopril, found ABP and SBP, but not OBP, predictive of changes in LV mass, simply by improved reproducibility of out of the office BP measurement (Mancia et al 1997). This has been further demonstrated in other clinical trials of both normotensive and hypertensive patients (James et al 1988, Palatini et al 1994, Zakopoulos et al 2001).

Daytime and night-time blood pressure can be thought to oscillate around a central point, the mean or average blood pressure. The degree of variation around the mean pressure can be expressed as a percentage, the coefficient of variation (Bland 1986). This is the best way to examine the degree of reproducibility of any blood pressure measurement, either within or between patients. Increasing the number of blood pressure measurements will improve reproducibility as evidenced by a smaller

coefficient of variation when compared to office measurements. Due to the relative inactivity of sleep, the coefficient of variation of nocturnal pressure should be smaller than daytime pressure, e.g. in the Syst-Eur trial – 8.7% vs. 10.4% for nighttime vs. daytime (Staessen et al 1999). Perhaps the reason that nocturnal pressure is more accurate in predicting cardiovascular outcomes is that this is the more reproducible pressure.

### ***Conclusions***

Within the last 10 years, there has been an enormous advance in our appreciation of the utility of out of the office blood pressure measurement. Given knowledge of the prevalence of masked hypertension and the prognostic superiority of out of office blood pressure measurement, diagnosis and management of hypertension using only office blood pressure readings is no longer an option. To do so will put patients at unnecessary risk.

### ***Hypothesis and Principle Aims***

The last ten years have seen an ever increasing body of evidence demonstrating out of office blood pressure is superior to office BP measurement in describing cardiovascular risk. The overarching hypothesis to be tested is that this superiority is a direct result of the method of measurement used. Not only does out of office measurement remove most of the causes of within-patient blood pressure variability outlined above, the number of measurements give a more statistically accurate reflection of mean blood pressure and therefore measurement is more reproducible.



The principle aims of this thesis were to examine the reproducibility of ABPM, in terms of daytime BP and reproducibility of nocturnal dip, and assess SBPM, particularly the level of agreement with ABPM and acceptance to patients. The direct clinical correlation was having demonstrated improved accuracy and reproducibility of BP using out of office BP measurement, there can be greater confidence in making clinical decisions, either in diagnosis or as a guide to antihypertensive medications.

### ***Outline of thesis***

The technique and indications for ambulatory blood pressure monitoring have been well established for over 10 years. Whilst there is a vast amount of literature documenting the advantages of ABPM in terms of prognosis, there is relatively little written on the reproducibility of ABPM in patients who are treatment naive and remain so on repeated assessments with ABPM. In chapter 2, I have examined ABPM reports on 512 patients who have had ABPM assessments on at least 2 occasions, both times free from antihypertensive drugs. This has allowed assessment of the reproducibility of blood pressure by 3 separate methods. Firstly, calculation of the coefficient of variation (repeatability coefficient) for ABPM as described by Bland and Altman (Bland 1986). Second, the reproducibility of blood pressure classification i.e. hypertensive or normotensive can be addressed using Cohen's kappa statistic. This is a relative statistic where a value of 1 denotes perfect reproducibility and 0 denotes no reproducibility. It is a better way of describing reproducibility than simple percentages as it takes into account what may have occurred by chance. Thirdly, the reproducibility of blood pressure as a continuous variable can be examined using the intra-class correlation coefficient (ICC) for unordered pairs. Again this is a relative statistic. This is used in



preference to Pearson's correlation coefficient for the following reason. With Pearson's coefficient, the product is different depending which value is input first i.e. if data from the first ABPM is input first and data from the second ABPM is input second, the value will be different if the data is input in the reverse order. With the ICC, there is no difference in the value of the product irrespective of which order the data is entered.

Furthermore, by sub-dividing the 512 subjects with repeat ABPM into different time intervals between monitoring episodes i.e. those with 2 episodes within six months, within 12 months etc up to those where the episodes are separated by 3 years, the stability of blood pressure was examined using the ICC and kappa statistic.

Nocturnal blood pressure dipping has a Gaussian distribution and lack of nocturnal dip has been associated with increased risk of cardiovascular disease. Although somewhat arbitrary, a systolic fall in BP of  $>10\%$  when sleeping defines a "dipper" and  $<10\%$  nocturnal fall defines "non-dippers". Unsurprisingly, such a dichotomous classification is problematic when examining reproducibility of nocturnal dip. Using the same cohort identified in chapter 2 and the same statistical analysis, chapter 3 examines the reproducibility of nocturnal blood pressure dipping when expressed both as a dichotomous and continuous variable and explores which is more clinically relevant.

It is well recognised that hypertension is poorly treated, with significant numbers never achieving blood pressure control. The advent of the new General Medical Services (nGMS) contract in 2004 has a specific subdivision for known hypertensive patients achieving BP control (defined as  $<150/90\text{mmHg}$ ). With the new added financial

incentive of the nGMS contract, it could be assumed BP control has improved, as suggested by QOF figures.

Previous work from our department has demonstrated that GPs only follow treatment recommendations, based on ABPM results, in 75% of cases. However, this was based on reporting of individual ABPM, not following specific guidelines. In chapter 4, I examined the level of blood pressure control one year after a definitive diagnosis of hypertension based on ABPM. With equal numbers pre and post implementation of the nGMS contract, there is scope to speculate whether or not the nGMS contract has improved therapeutic aggressiveness and if the number achieving BP control matches the nationally quoted statistics.

In terms of preventing macrovascular disease and progression of renal disease, the importance of aggressive and consistent blood pressure control in patients with type 2 diabetes cannot be understated. For this reason, a novel, pharmacist-led cardiovascular risk clinic was set up in our unit for patients who did not achieve target blood pressure during 'usual care' at the diabetes clinic and primary care. In chapter 5 I have examined the efficacy of the clinic in terms of reducing blood pressure and lipids. Also, the long term blood pressure lowering effects, as judged by ABPM, was assessed in those patients discharged for more than 6 months from the 'intensive' clinic set up.

All ABPM reports in our unit are reported by a single clinician. By chance, the same report was assessed twice, with different advice given. This has led to a series of projects examining the intra and inter-observer concordance of reporting of ABPM reports. In theory, with both European and American hypertension societies defining hypertension as a daytime ABPM average of  $> 135/85\text{mmHg}$ , there should be little

disagreement amongst experts. Preliminary work demonstrated poor concordance of opinion amongst local experts when reporting ABPM. Therefore, international experts in hypertension were provided with identical raw ABPM data in a series of studies which investigated concordance of opinion in terms of diagnosis and management strategies. Chapter 6 details these results, and compares 'expert' opinion to computer-based diagnosis.

Whilst ABPM has many benefits, problems do exist. ABPM is still a relatively expensive technology, requiring additional training of medical and nursing staff, and not appropriate for widespread use in primary care. The principal disease burden of hypertension exists in primary care, not to mention the yet undiscovered masses with masked hypertension. For all these reasons, a possible solution may be self monitored blood pressure.

In chapter 7 I have taken a group of patients referred for ABPM and compared their daytime average BP to average BP obtained from a week of SBPM, as described by the ESH guidelines. The difference in mean pressures and diagnostic categorisation are discussed, as well as patient preference.

## Chapter 2

### ***The Demographics of Hypertension and Blood Pressure Reproducibility***

#### ***Background***

The ambulatory blood pressure service has been running at the Western General, Edinburgh since 1997 (Richards *et al* 2004). To date, approximately 15,000 ABPM assessments have been carried out; with the vast majority of these “direct access” i.e. GP’s refer patients to the service without patients being reviewed in secondary care. The 15,000 episodes include 10,516 subjects with a single ABPM assessment, of which approximately half were on no antihypertensive agents at the time of ABPM (n=5,167). Of the 1,845 subjects with 2 ABPM assessments, 512 were free from antihypertensive medications on both occasions, allowing opportunity to examine the reproducibility of 24-hour blood pressure measurement and the reproducibility of nocturnal dipping, expressed as a dichotomous and continuous variable (Chapter 3). Even taking into account a degree of selection bias, this is a uniquely large population.

#### ***Aim***

To describe prevalence of white coat hypertension, masked hypertension and true hypertension in an open access ABPM service. In addition, investigate different methods of describing reproducibility of blood pressure measurement i.e. as a continuous or dichotomous variable.

#### **Blood pressure measurement**

ABPM is performed using a validated, non-invasive oscillometric device - Spacelabs 90207 or 90217 (O’Brien *et al* 1991), which has been used exclusively throughout and

remain accurate with regular calibration after 10 years of use (Amoore *et al* 2005). The standard operating procedure for the monitoring is as follows: The appropriate sized cuff was used and blood pressure taken, initially in both arms. If a significant difference exists between the arms ( $>10\text{mmHg}$ ), the arm with higher pressure was used. Repeat ABPM, if required, was done using the same arm. If there is no significant difference, the non-dominant arm was used. BP is recorded at 30 minute intervals throughout the following 24 hours, with day and night defined by patient diaries (Stewart 1993). Raw blood pressure data are then downloaded and stored in a Microsoft Access database. Editing criteria are the default criteria from the Spacelabs software (readings excluded if systolic BP  $>260\text{mmHg}$  or  $<70\text{mmHg}$ , diastolic BP  $>150\text{mmHg}$  or  $<40\text{mmHg}$  and / or pulse pressure  $>150$  or  $<20$ ). Patients with atrial fibrillation are not assessed by ABPM. If diaries are not returned, night-time defaults to 10pm to 8am.

GPs receive a report with graphical representation of the 24-hour blood pressure, the mean awake, mean sleep blood pressure and the calculated nocturnal blood pressure dip (appendix 1). The clinician in charge of the service includes a comment on whether or not treatment is indicated or should be changed.

### ***Demographics of the untreated population (n=5,167)***

During the 24 hours of ambulatory measurement, 79% of subjects (n=4061) had 48 valid blood pressure readings. Sleep quality was reported as poor in 9%, not commented on in 0.5% with the rest reporting good quality of sleep. The age of patients referred was normally distributed with a mean age of  $47.7 (\pm 14.4)$  years old, 47% male. The “office” blood pressure (OBP) measured by the GP prior to referral for ABPM is not recorded in the database therefore “OBP” refers to the first BP recorded with the

oscillometric device. The mean office BP, awake BP, and asleep BP are in table 2.1 with the distribution of office and daytime systolic and diastolic pressures seen in figures 2.1 and 2.2 respectively.

All pressures are mean  $\pm$  SD unless otherwise stated. Hypertension is defined as office BP  $\geq 140/90$ mmHg (Williams et al 2004) and out of office BP  $\geq 135/85$ mmHg (O'Brien et al 2005).

Figure 2.1 – Office and awake-time mean systolic blood pressure of 5,167 patients on no antihypertensive treatment at first assessment with ABPM

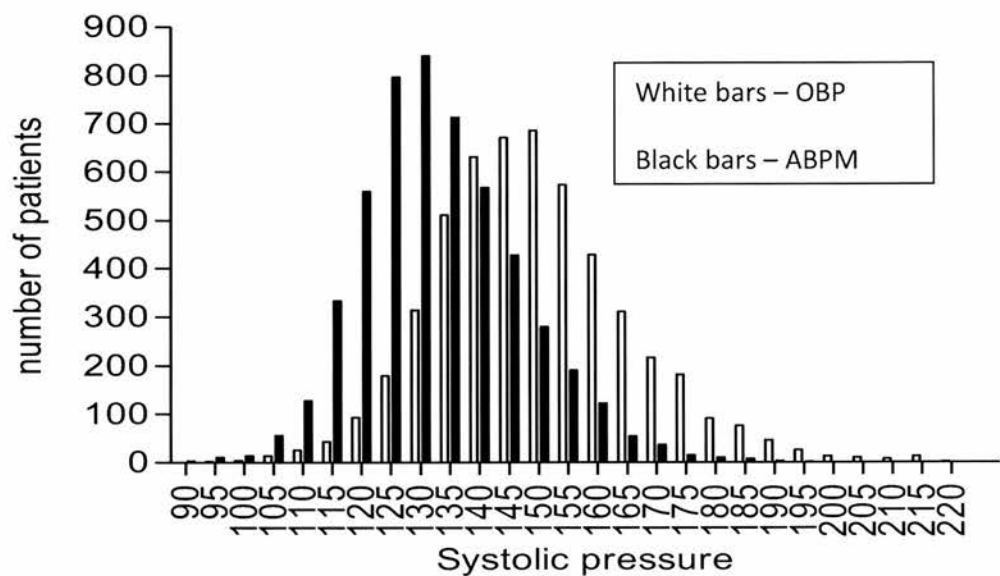


Figure 2.2 – Office and awake-time mean diastolic pressure of 5,167 patients on no antihypertensive treatment at first assessment with ABPM

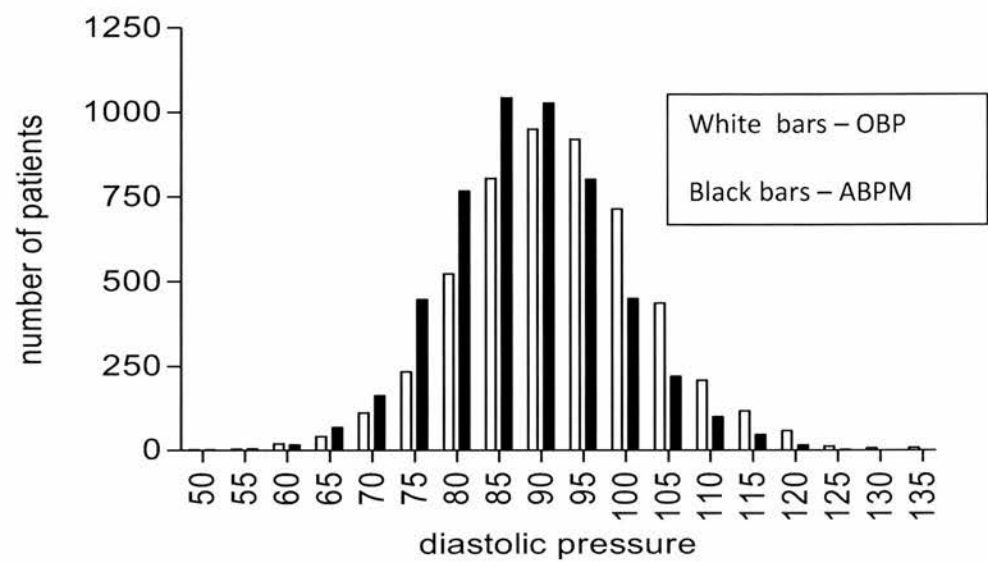


Table 2.1 Mean ( $\pm$ SD) BP values of 5,167 patients on no antihypertensive treatment at time of first ABPM

	Systolic	Diastolic
Office	149.5 $\pm$ 16.7	92.2 $\pm$ 11.3
ABPM – day	143 $\pm$ 13.7†	88.1 $\pm$ 9.9†
ABPM - night	120.9 $\pm$ 18.7	71.5 $\pm$ 12.3

† p<0.001 comparing office to daytime ABPM

Of the 5,167 untreated patients referred, 20% (1,031 subjects) were normotensive on office BP. In half of these subjects, ABPM confirmed true normotension (10.5% / 539 subjects) while the others had masked hypertension (9.5% / 492 subjects). White coat

hypertension was present in 8.5% (438 subjects) and the remaining 71.5% (3698 subjects) had true hypertension.

Those with true hypertension are significantly older than all other categories ( $p < 0.001$ ). There is no significant age difference between the masked or white coat hypertensive groups and the normotensive group are significantly younger than those with WCH ( $p = 0.002$ ) and masked hypertension ( $p = 0.028$ ) (table 2.2).

#### *Nocturnal Dipping in the untreated population*

Nocturnal blood pressure data are available for 5,103 of the 5,168 untreated patients. The mean nocturnal dip was  $14.4 \pm 6.3\%$ . If 'dippers' are defined as having a nocturnal blood pressure fall of  $\geq 10\%$ , 78% of the untreated population are 'dippers'. This can be further subdivided to assess the likelihood of dipping in the normotensive, WCH, masked hypertensive and true hypertensive populations (table 2.2) and also examined with an age cut-off (table 2.3) and by decade (table 2.4). Each decade was further subdivided into male and female to see if there was any sex preponderance in dipping. In the age group  $< 30$ , 76% of females and 84% of males are dippers. In the 30-40 year old group, 77% of females and 84% of males are dippers. In all other age categories, there was no more than a 2% difference in dipper classification between males and females.



Table 2.2 – Blood pressure details for the 5,167 untreated patients with normal BP, White coat hypertension, masked and true hypertension

	Office BP		ABPM awake average		Mean age	Males	% dippers
	Systolic	Diastolic	Systolic	Diastolic			
Normal	127.9±8.7	79.1±6.7	125.1±6.4	76.9±5.5	44.8±17.5	34%	80
WCH	145.4±9.2	88.8±8.4	127.9±8.9	77.8±6.7	47.6±14.6	36%	74
Masked HBP	131.6±6.4	82.8±5.6	137.8±6.7	86.4±5.9	46.7±13.6	48%	74
True HBP	155.5±14.6	95.7±10.4	148.1±11.8	91.2±9.1	51.1±13.8	50%	81

Table 2.3 Incidence of non-dipping in the untreated population as per blood pressure category (normal,WCH,masked or hypertensive), sex & age

	Female<50	Male<50	Female>50	Male>50
Normotension	29% (63)	27% (31)	30% (39)	39%(26)
WCH	24% (36)	23% (21)	26% (33)	36% (21)
Masked	25% (37)	22% (31)	32% (33)	27% (25)
Hypertension	17% (137)	15% (136)	22% (223)	23% (211)

Key: numbers in brackets are absolute numbers in each group

Table 2.4. Mean office and ambulatory BP ( $\pm$ SD) & mean nocturnal dip ( $\pm$ SD) by age (decade) within the untreated population (n=5,167)

Total no.subjects		459	814	1186	1309	886	418
Age		<30	30-39	40-49	50-59	60-69	>70
OBP	Systolic	141( $\pm$ 13)	144( $\pm$ 13)	148( $\pm$ 15)	151( $\pm$ 17)	155( $\pm$ 18)	159( $\pm$ 19)
	Diastolic	88( $\pm$ 11)	93( $\pm$ 10)	95( $\pm$ 11)	93( $\pm$ 11)	91( $\pm$ 11)	87( $\pm$ 12)
ABP awake	Systolic	137( $\pm$ 11)	139( $\pm$ 11)	142( $\pm$ 12)	144( $\pm$ 14)	147( $\pm$ 14)	150( $\pm$ 15)
	Diastolic	85( $\pm$ 10)	89( $\pm$ 9)	91( $\pm$ 9)	89( $\pm$ 9)	86( $\pm$ 10)	82( $\pm$ 9)
ABP asleep	Systolic	118( $\pm$ 11)	119( $\pm$ 11)	120( $\pm$ 13)	122( $\pm$ 13)	126( $\pm$ 14)	132( $\pm$ 17)
	Diastolic	67( $\pm$ 9)	72( $\pm$ 10)	74( $\pm$ 10)	73( $\pm$ 9)	72( $\pm$ 10)	71( $\pm$ 10)
Mean dip		14( $\pm$ 5)	14( $\pm$ 5)	15( $\pm$ 6)	15( $\pm$ 6)	14( $\pm$ 7)	11( $\pm$ 8)
% 'dippers'		80	81	82	81	76	60

### ***Regression analysis for predictability of nocturnal dipping***

Linear regression analysis was carried out using age and systolic blood pressure versus actual percentage nocturnal dip as a continuous variable. The correlation for age was poor ( $r=-0.07$ ) and only marginally better for systolic BP ( $r=0.13$ ). Neither of these was usefully predictive.

In terms of predicting dipping as a dichotomous variable (yes/no), multivariate binomial regression demonstrated a significant univariate correlation for both age and systolic BP ( $p<0.001$ ). This was then inserted into an odds ratio equation to predict the percentage chance of each subject being a 'dipper'. The turning point was 0.78 – below this, 73% of subjects were dippers and above this value 82% of subjects were dippers. This demonstrated poor discriminatory power for the variables analysed (age, sex, awake-time mean systolic pressure).

### ***Effects of antihypertensive drugs***

Within the database, there were 284 patients with 2 ABPM episodes, the first ABPM on no antihypertensive medication and the second ABPM on antihypertensive medication. Unfortunately due to limitations of the database, this can only be classified as 'antihypertensive medications', without being more specific about drug classes. Table 2.5 demonstrates the changes in OBP, awake and nocturnal BP between assessment one and assessment two. All changes between assessments were highly significant ( $p < 0.001$ , significance tested with students paired T-test). It was interesting to see the fall in OBP and awake ABP is not substantially different. Proponents of only using OBP often quote all of the endpoint trials in treatment of hypertension are based on OBP, not ABP. The data shows the true fall in BP is as suggested by OBP, only that the start and end points are lower.

Table 2.5. Office and ABPM values in 284 patients before and after antihypertensive treatment was commenced

		Pre treat	Post treat	Mean ▲
Office	Systolic	165(±22)	149(±17)	16
	Diastolic	100(±12)	89(±12)	11
Awake	Systolic	155(±15)	140(±13)	15
	Diastolic	94(±10)	84(±10)	10
Nocturnal	Systolic	132(±17)	122(±16)	10
	Diastolic	80(±11)	70(±10)	10

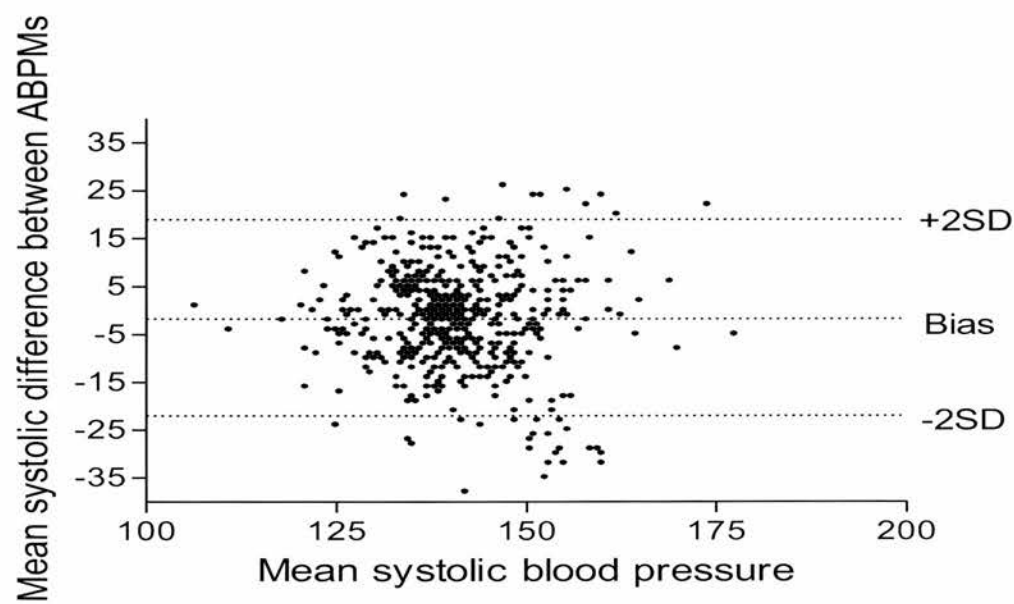
***Reproducibility of blood pressure measurement***

Within the ABPM database, there were 512 patients with 2 separate ABPM episodes who had never been treated with antihypertensive medications. The mean time between ABPM episodes was 29 months (± 19). Of these, 55 subjects underwent further monitoring, with 44 months (±22) between the first and third ABPM studies. The mean blood pressures from each episode were used to calculate the coefficient of variation for ABPM - table 2.6 and figure 2.3.

Table 2.6 – Coefficient of variation (CV) derived from 512 treatment naive patients with two ABPM and 55 patients with three ABPM

	1 <sup>st</sup> & 2 <sup>nd</sup> ABPM				1 <sup>st</sup> , 2 <sup>nd</sup> & 3 <sup>rd</sup> ABPM			
	Awake		Sleep		Awake		Sleep	
	Systolic	Diastolic	Systolic	Diastolic	Systolic	Diastolic	Systolic	Diastolic
CV	5.9	6.2	6.6	7.7	6.5	6.4	6	7.5
(95% CI)	(5-6.7)	(5.5-6.9)	(5.9-7.2)	(7-8.3)	(5.6-7.4)	(3.9-8.2)	(5.2-6.9)	(6.4-8.5)

Figure 2.3 – Bland Altman plot for systolic pressure in 512 patients with repeat ABPM



If the office blood pressure was disregarded, thereby removing the categories of white coat hypertension and masked hypertension, the awake ABP can be used to classify subjects as hypertensive or not. The kappa value of 0.28 for repeat ABPM indicated relatively poor reproducibility of classification. This was further sub-divided into those

with repeat ABPM within 6 months (n=42), 6 -12 months (n=54), 12-24 months (n=137), 24-36 months (n=125) and greater than 36 months (n=154) (table 2.7). Similarly, the intra-class correlation coefficient and coefficient of variation can be calculated for each of these time intervals (Tables 2.8 and 2.9 respectively).

Table 2.7. Kappa values for reproducibility of hypertensive / normotensive classification in 512 treatment naive subjects with 2 episodes of ABPM

	Time interval between episodes of ABPM				
	0-6 months	6-12 months	12-24 months	24-36 months	>36 months
Kappa (OBP)	0.26	0.35	0.19	0.18	0.15
Kappa (ABPM)	0.55	0.47	0.04	0.36	0.22

Table 2.8. Intra-class correlation coefficients for both OBP and ABP in 512 treatment naive subjects

		Time interval between episodes of ABPM				
		0-6 months	6-12 months	12-24 months	24-36 months	>36 months
ICC (OBP)	Systolic	0.57	0.54	0.43	0.51	0.59
ICC (OBP)	Diastolic	0.72	0.25	0.67	0.62	0.56
ICC (ABP)	Awake Systolic	0.69	0.40	0.39	0.57	0.59
	Awake Diastolic	0.80	0.56	0.75	0.78	0.74
ICC (ABP)	Sleep Systolic	0.71	0.66	0.72	0.72	0.66
	Sleep Diastolic	0.77	0.65	0.83	0.79	0.66

Table 2.9. Coefficient of Variation (CV) for OBP and ABP in 512 treatment naive subjects

		Time interval between episodes of ABPM				
		0-6 months	6-12 months	12-24 months	24-36 months	>36 months
CV (OBP)	Systolic	7.1	7.6	8.2	6.7	7.9
CV (OBP)	Diastolic	7.7	10.6	7.8	7.2	8.7
CV (ABP)	Awake Systolic	6.2	6.1	6.4	5.0	6.1
	Awake Diastolic	7.0	6.6	6.3	5.4	6.5
CV (ABP)	Sleep Systolic	6.4	6.4	6.0	6.0	7.5
	Sleep Diastolic	8.3	9.1	6.6	6.5	8.8

Nocturnal dipping can be expressed either as a dichotomous (dipper/non-dipper) or continuous (percentage fall in nocturnal BP) variable. The reproducibility of the nocturnal dip and whether this is affected by antihypertensive treatment is addressed in chapter 3.

**Discussion**

Assessment of this large dataset aimed to investigate several key areas of specific clinical interest. Within the local population, how does the prevalence of white coat and masked hypertension compare with the published data (Sega 2001, Ohkubo 2005); what is the distribution of nocturnal dipping, and is this affected by age, sex and BP classification (hypertensive, masked hypertensive, white coat hypertension and normotension); how does office BP compare with ABP; and what is the most reproducible way of describing BP.

The prevalence of white coat hypertension and masked hypertension was lower than previously described (Sega 2001, Ohkubo 2005). There are a couple of explanations for the discrepancy with the published literature. There is little evidence regarding why patients are referred from primary care for ABPM but it is likely stimulated by high office BP measurement. The office BP quoted represents the first BP measurement taken with the Spacelabs oscillometric device immediately prior to ABPM as unfortunately the referral BP is not recorded in the database. As already discussed, doctor measured BP is substantially higher than true BP therefore when BP is measured to a reliable standard using the oscillometric device operated by nursing staff, the white coat effect will be smaller (Little et al 2002, Head et al 2010). This may also explain the mean difference between office BP and mean daytime BP (6/4mmHg) being smaller than the expected average difference of 10/5mmHg (Williams 2004) but more in keeping with the mean difference reported by Head et al when OBP is measured by non-medical staff. In addition, if high OBP in primary care is the main stimulus for referral for ABPM, this will explain the lower incidence of masked hypertension.

BP rises with age and table 2.4 examines this in more detail. The systolic pressure rises progressively with age although the diastolic pressure rises until age 50 then falls i.e. pulse pressure increases from age 50 onwards. This is true for office, awake and asleep BP. The difference between office and ABP progressively increases as age increases, from 4/3mmHg in subjects <30 to 9/5mmHg in those >70 years old.

Dipping can be analysed as either a dichotomous or continuous variable. The reproducibility of each method is described in the following chapter however for those patients with a single ABPM, it can be seen that rates of dipping are similar across the



age spectrum until age 70 is reached. Another way to examine nocturnal dipping is to subdivide the subjects by category of blood pressure i.e. normotensive, WCH etc. In addition, an age cut-off of 50 was chosen as there were approximately equal numbers younger or older than this age. Males, but not females, with normal BP or WCH exhibit a substantial increase (12-13%) in rates of non-dipping with an apparent cut-off at age 50. Within the masked and true hypertensive groups, both sexes exhibit increased rates of non-dipping after age 50, albeit less marked (7-8%).

As mentioned in the introduction, blood pressure measurement is imprecise: we are attempting to indirectly measure a physiological variable which changes in a beat to beat fashion. It is therefore unlikely that any two measurements will be the same. Clinically, this is most obvious on casual office measurements. It is not unusual for BP values to vary by 20-30mmHg on sequential visits, without any therapeutic intervention. The question arises, therefore, as to whether any other means of measuring blood pressure is more reproducible.

Reproducibility of blood pressure is essentially a question of how accurate a method is of estimating 'true' mean BP. As the number of blood pressure readings increase, the more likely the mean will represent true blood pressure and therefore ABPM should be more reproducible than OBP (James 1988). Within the rigorous standards of a clinical trial, or dependent on the circumstances of BP measurement, OBP can have the same degree of reproducibility as ABPM (Jula 1999, Warren 2008, Myers 2009). Using the coefficient of variation from this dataset where 'office BP' was taken within the blood pressure unit using an oscillometric device under controlled circumstances, it can be seen there is no difference to the CV of ABPM. However, routine clinic measurements

have a CV of 12-14% (Warren 2008), demonstrating poorer reproducibility than ABPM in routine clinical practice.

Without doubt, the most useful information extracted from this database lies within the subgroup of 512 never-treated subjects with 2 episodes of ambulatory monitoring. Subdividing these subjects by time intervals between their episodes of ABPM allowed assessment of the most 'stable' measurement of BP, and indeed which BP (day/night/systolic/diastolic) is most reproducible. The repeatability coefficient (Bland 1986) is arguably the most widely used method of assessing reproducibility of BP measurement. In addition, it can be assessed as a continuous or dichotomous variable, using the intra-class correlation coefficient and Cohen's Kappa statistic respectively. When the kappa statistic was applied to the reproducibility of classification of hypertension, the value of 0.28 demonstrates reproducibility of the dichotomisation of BP is relatively poor. When the time interval between episodes of monitoring is taken into account, there is moderate reproducibility with measurements taken within a year but this declined with increasing time between episodes. However, when BP is assessed as a continuous variable, the ICC indicated improved reproducibility (as the value is closer to 1 compared to kappa) and more importantly, the ICC remained stable independent of the time interval between episodes of ABPM i.e. is a more reproducible measure of blood pressure.

In conclusion, blood pressure is a continuous variable which rises with age, as does the difference between office and ambulatory blood pressure.

Dichotomisation of BP status as hypertensive or normotensive is poorly reproducible, especially over long periods of time whereas BP is stable over time when expressed as

a continuous variable. This provides evidence for the recommendation made at the Sir George Pickering lecture at the 2008 British Hypertension Society meeting where it was suggested that the dichotomisation of patients into hypertensive and normotensive should be abandoned. Instead, an individual's BP should be addressed as a continuous, rather than dichotomous variable, now demonstrated to have improved reproducibility over time. In conjunction with other risk factors, this assigns their cardiovascular risk and therefore determines who should receive antihypertensive treatment.

## Appendix 2.1. Sample ABPM report.

The Lothian University  
Hospitals NHS Trust

Western General Hospital



Cardiovascular Risk Clinic  
Blood Pressure Monitoring Report

Tel: 0131 537 2473

Fax: 0131 537 1493

### GP Details

Dr JR ROBERTSON  
MUIRHOUSE MEDICAL GROUP  
1 MUIRHOUSE AVENUE  
EDINBURGH

### Patient Details



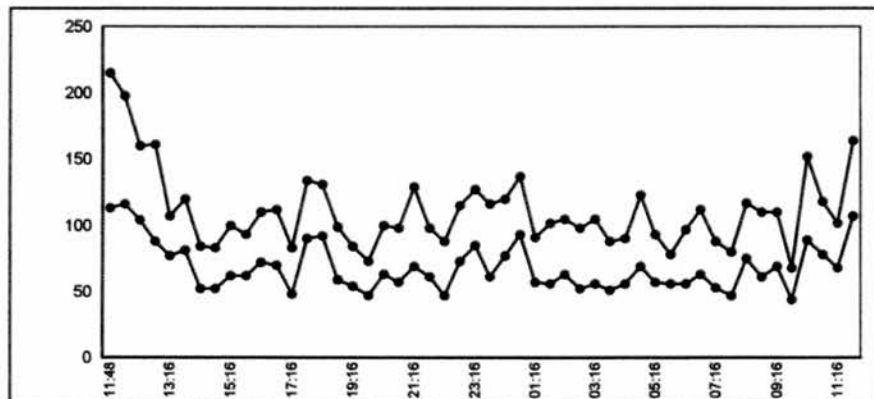
Referring Dr: Dr Panarelli, SpR in Clin Biochem.

ID No [REDACTED]

### Current Medication

	Dose	Frequency
Bendrofluazide	2.5mg	od
Diltiazem	90mg	bd
Simvastatin	1 sachet	od
HRT		
Co proxamol	2 tab	PRN

Below is an ambulatory BP report on your patient. The graph is displayed for information and to allow demonstration to the patient but the most important figure to consider is the awake time average (calculated on the basis of the patient's diary entry). In general, treatment is recommended if the awake/day average is  $\geq 145/95$ . Whereas a figure of  $\leq 135/85$  should be considered normal (or well controlled if on therapy). The sleep/nighttime pressure may influence management if there is little or no reduction of BP with sleep. Specific comments for the patient can be seen below.



### BP Results

Start date: 27/07/1998

#### Initial BP Recording:

215/113 left  
right

#### Average BP (awake)

116/72

#### Average BP (asleep)

104/62

#### Nocturnal BP Dip

10.3/13.9 %

Monitoring: 100 % Successful: No of Readings: 50 Sleep quality: Good

Cuff size: Standard

### Comments

Reported by:

Date:

## Chapter 3

### ***The reproducibility of nocturnal dipping***

#### *Background*

The observation that blood pressure levels fall during sleep was first made by Sir George Pickering, in 1964, using intra-arterial blood pressure measurements (Richardson et al, 1964). The subsequent development of non-invasive 24-hour ambulatory blood pressure monitors (ABPM) has allowed investigation of the significance of this observation on a much larger scale. O'Brien first coined the term "dipping" (originally a nocturnal blood pressure fall of  $>10/5$ mmHg) and explored its relationship with cardiovascular disease (O'Brien et al 1988).

The traditional dichotomous classification of nocturnal dip is dependent on arbitrary criteria and poorly reproducible (Parati et al 2007). Within the published literature, dipping is variably defined using systolic and diastolic pressure (Mochizuki et al 1998, Cuspidi et al 2007, Hernandez Del-Rey 2007), systolic pressure alone (Ben Dov et al 2005), "BP" with no further clarification (Palatini et al 1994, Omboni et al 1998, Manning et al 2000, Chaves et al 2005) or day/night ratio (Rahmana 2005, Boggia 2007). Similarly, day and night definitions are variable, using either fixed times (Palatini et al 1994, Omboni et al 1998, Cuspidi et al 2007) or patient diaries (Mochizuki et al 1998, Manning et al 2000, Ben-Dov et al 2005, Chaves 2005, Hernandez Del-Rey et al 2007). It is not surprising that reproducibility of blood pressure dipping varies dependent on which definition is employed (Heskens et al 2008).

However, if nocturnal fall in blood pressure is expressed as a continuous, rather than a dichotomous variable, it may be more reproducible (Chaves et al 2005) and clinically relevant in relation to cardiovascular disease (Boggia 2007).

## ***Hypothesis***

Nocturnal blood pressure dipping does not change significantly over time and the current literature reporting poor reproducibility is a result of dichotomizing a continuous physiological variable.

## ***Aim***

The study aim was to examine reproducibility of nocturnal fall in BP and demonstrate the improved reproducibility when dipping is expressed as a continuous rather than dichotomous variable.

## ***Methods***

Patients were identified through the hospital ABPM database (described in chapter 2). Subjects undergoing ABPM on at least 2 occasions were identified and those with any current or previous exposure to antihypertensive medications were excluded from analysis. In common with many authorities, subjects with < 80% successful readings were also excluded (n=3).

The sleep/wake times as recorded in the patients' diaries describe daytime and night-time (Stewart et al 1993), allowing calculation of average daytime and average nocturnal blood pressure. Only systolic nocturnal dip was examined (Williams et al 2008) and was defined as  $((\text{awake systolic} - \text{asleep systolic}) / \text{awake systolic}) \times 100$  with  $\geq 10\%$  nocturnal dip regarded as a "dipper", in keeping with most of the published literature (Verdecchia et al 1990, Cuspidi et al 2007). The absolute difference in hours of sleep between first and second ABPM was calculated, in addition to percentage fall in

nocturnal BP to examine whether or not duration of sleep was contributory to any change in dip.

**Statistics**

Reproducibility of dipping as a dichotomous variable (dipper/non-dipper) is described by percentage, to be more confluent with existing literature, and using Cohen’s Kappa statistic ( $\kappa$ ). Reproducibility of dipping as a continuous variable is assessed using the intra-class correlation coefficient (ICC) for pairs of measurements i.e. percentage of nocturnal dip on ABPM 1 and ABPM 2 (Bland et al 1996). Both are relative statistics, taking into account what would be expected by chance, with a value of 1 denoting perfect agreement (reproducibility) and 0 denoting no agreement. All results are mean  $\pm$  SD

**Results**

There were 512 never-treated subjects identified with ABPM assessments on 2 separate occasions, a mean of 29 months ( $\pm$  19) apart (table 3.1). The mean age at initial referral was 48 ( $\pm$ 14 SD) yrs and 42 % of the study population were male.

Table 3.1. Baseline data of 512 subjects studied for reproducibility of nocturnal blood pressure fall

	Awake BP		Nocturnal BP		Sleep duration (hr/min) (IQ range)	No. successful readings over 24 hours ( $\pm$ SD)	Sleep quality 'good'
	Systolic ( $\pm$ SD)	Diastolic ( $\pm$ SD)	Systolic ( $\pm$ SD)	Diastolic ( $\pm$ SD)			
ABPM 1	140( $\pm$ 10)	88( $\pm$ 9)	120( $\pm$ 12)	72( $\pm$ 9)	7.45(6.35-9)	49 ( $\pm$ 2)	93 %
ABPM 2	142( $\pm$ 10)	88( $\pm$ 9)	122( $\pm$ 12)	73( $\pm$ 9)	8(7.20-11.30)	49( $\pm$ 2)	89%

### *Dipping as a dichotomous variable.*

In total, 76% (392 of 512 subjects) retained their original dipping status. Of the 405 subjects who dipped on the first ABPM, 85% (345 subjects) dipped on the second ABPM and of the 107 who did not dip on the first ABPM, 44% (47 subjects) remained non-dippers on the second ABPM,  $\kappa=0.29$ . This can be further sub-divided into those patients with 2 ABPM assessments within: (a) six months – 42 subjects, (b) six months to one year – 54 subjects, (c) 1 to 2 years – 137 subjects, (d) 2 to 3 years – 125 subjects and (e) more than 3 years – 154 subjects. The kappa values for these time intervals are found in table 3.2.

In the 55 subjects with 3 ABPM assessments, 58% (32 subjects) dip on all 3 occasions whilst 4% (2 subjects) do not dip on all 3 occasions. The number of subjects is too small to make any statement about time intervals.

### *Dipping as a continuous variable*

Blood pressure is distributed normally in populations, as is the percentage nocturnal fall in BP (Staessen et al 1997). I have thus examined the data as a continuous variable. Figure 3.1 demonstrates the distribution of nocturnal dip during the first and second ABPM recordings respectively.



Table 3.2 Reproducibility of dipping with different time intervals between ABPM assessments

Interval (months)	Subjects	T1=D, T2=D	T1=D, T2=ND	T1=ND, T2=D	T1=ND, T2=ND	Kappa	ICC
0-6	42	52% (n=22)	17% (n=7)	17% (n=7)	14% (n=6)	0.22	0.59
6-12	54	70% (n=38)	15% (n=8)	11% (n=6)	4% (n=2)	-0.14	0.70
12-24	137	73% (n=100)	9% (n=12)	10% (n=14)	8% (n=11)	0.34	0.60
24-36	125	66% (n=83)	10% (n=13)	12% (n=15)	11% (n=14)	0.36	0.60
>36	154	64% (n=100)	16% (n=24)	12% (n=18)	8% (n=13)	0.21	0.59

Legend

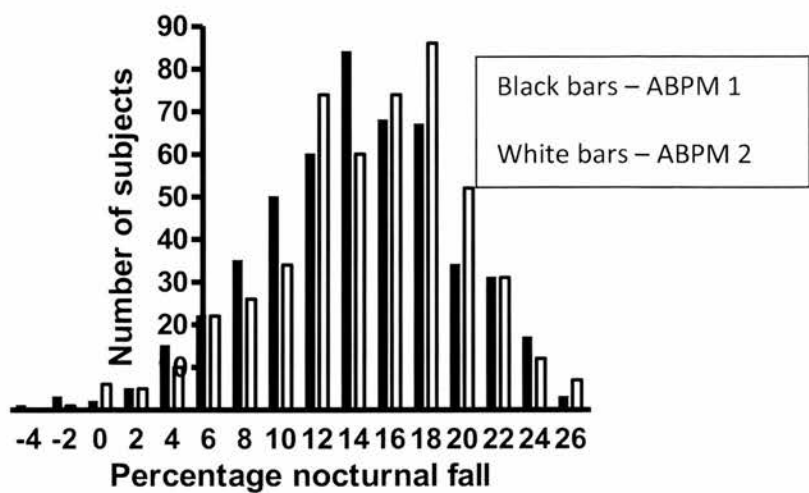
T1=D – Dipper on 1<sup>st</sup> ABPM, T1=ND – Non-dipper on 1<sup>st</sup> ABPM

T2=D – Dipper on 2<sup>nd</sup> ABPM, T2=ND – Non-dipper on 2<sup>nd</sup> ABPM

Kappa statistic refers to dipper/non-dipper repeatability i.e. dichotomous variable.

ICC=intra-class correlation coefficient refers to repeatability of dipping when expressed as a continuous variable.

Figure 3.1 Distribution of percentage fall in nocturnal blood pressure in 512 patients with repeated ABPM assessments



The mean nocturnal dip is 14% (SD  $\pm$  5) for both ABPM 1 and ABPM 2. For each subject, the amount their nocturnal dip changes from ABPM 1 to ABPM 2 can be measured, and expressed as percentage change e.g. if the nocturnal dip in ABPM 1 is 12% and the nocturnal dip in ABPM 2 is 8%, the absolute change in dip is 4%. When comparing the two ABPM assessments in all subjects, the absolute difference is positively skewed with median absolute change in dip of 3.8% (IQ range 1.9-6.3%), graph 3.2. The duration of sleep did not have any effect on the median change in nocturnal dip, table 3.3 (derived from data of 462 patients due to incomplete records detailing quality of sleep in the remaining 60). Using the intra-class correlation coefficient for percentage change in dip in all subjects, its value is 0.6, indicating moderate agreement.

When this is sub-divided into different time intervals between ABPMs (within six months, six months to one year, 1 to 2 years, 2 to 3 years and >3 years), the intra-class correlation coefficient does not change substantially (table 3.1).

Figure 3.2 Change in nocturnal fall between ABPM 1 and ABPM 2

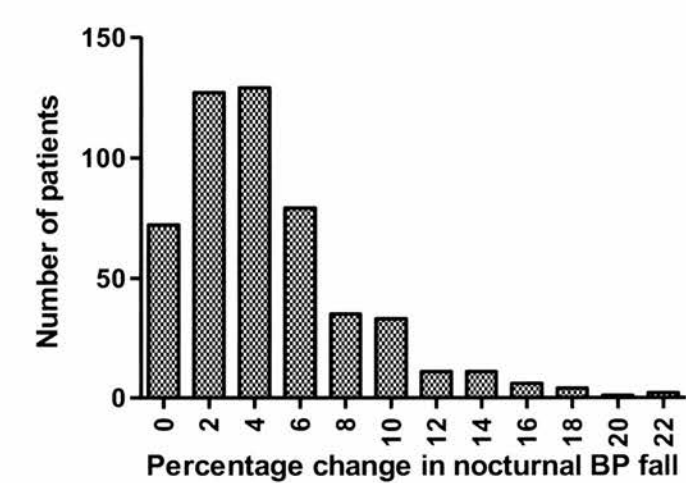


Table 3.3 The effect of varying sleep times on median percentage change in nocturnal BP dip

Difference in number of hours sleep between ABPM 1 and 2	Number of patients	Median percentage change in nocturnal dip (±IQ range)
<1 hour	260	3.8 (2-19.6)
1-2 hours	125	3.4 (1.6-17.9)
2-3 hours	47	4.3 (1.9-18.7)
3-5 hours	30	3.7 (3.1-17.1)

### *The effect of antihypertensive treatment on nocturnal dip*

There was data on 282 subjects who had antihypertensive treatment instituted after the first ABPM. Therefore, any systematic changes in dip as a result of treatment could be assessed. In total, 75% (n=212) did not change dipping category - 63% stayed as dippers (n=178) and 12% remained non-dippers (n=34),  $\kappa=0.33$ . The mean awake and nocturnal pressures for ABPM 1 (no treatment) and ABPM 2 (on treatment) can be found in table 2.5 (chapter 2). The mean nocturnal dip in ABPM 1 was calculated as 15% ( $\pm 7$ ) and 13% ( $\pm 7$ ) in ABPM 2, ICC 0.55 (95% CI 0.34-0.69). When ABPM 1 (no treatment) is compared to ABPM 2 (on treatment), the change in nocturnal dip is positively skewed with a median value of 4.4%.

### **Discussion**

This retrospective analysis aimed to demonstrate, in one of the largest untreated cohorts to be reported on, the reproducibility of nocturnal blood pressure dipping when examined as both dichotomous and continuous variables. Initially, reproducibility of dipping as a dichotomous variable seemed to be reasonably good and consistent with existing literature. However, given that most patients are 'dippers', chance dictates that a substantial percentage will dip on both occasions. The kappa value of 0.29 indicated poor reproducibility when the element of chance is removed. Also, the large variation in the kappa value when comparing dipping at different time intervals demonstrated this is a relatively poor way of quantifying nocturnal blood pressure fall. When dipping was examined as a continuous variable, the intra class correlation coefficient had a value of 0.6, indicating moderate agreement. The stability of this measurement was remarkably

independent of the time interval between episodes of ambulatory monitoring. Therefore, whilst not perfect, expressing nocturnal blood pressure fall as a continuous variable is substantially better than that of the dipper/non-dipper classification.

It is worth discussing the importance of sleep duration when calculating nocturnal blood pressure dip and therefore how this may impact on reproducibility. There is increasing understanding of the complex physiology involved in the nocturnal reduction in blood pressure. Evidence exists that nocturnal BP fall is a result of neural regulation mediated primarily through decreased sympathetic outflow, therefore reduction in both heart rate and vasomotor tone (Sayk et al 2007). However, this is not static during sleeping hours as there is increased sympathetic outflow during REM sleep as well as in other pathological states e.g. obstructive sleep apnoea. This becomes important when duration of sleep is considered and how sleep is defined i.e. by patient diary or fixed time periods, which can exclude transition phases such as going to sleep or during the morning surge. This chapter has defined nocturnal BP according to patient diaries, accepting there may be a transition phase at either end of 'sleep' which may artificially elevate estimation of the true nocturnal pressure. The median duration of sleep over both periods of monitoring was seven hours 45 minutes in ABPM 1 and eight hours in ABPM 2, representing 15-16 blood pressure measurements. It is arguable whether or not two blood pressure readings during the transition phases of wake to sleep and sleep to wake make a significant impact on the mean nocturnal blood pressure, an average of 16 measurements. The evidence presented in table 3.3 demonstrated there was no significant difference in percentage change in nocturnal BP dip in relation to varying duration of sleep. It is analogous to removing the 'white coat window' (O'Brien et al

1991) from ABPM readings, which does not significantly change the average daytime blood pressure on ABPM (chapter 7).

There is no universally accepted definition of nocturnal hypertension or method of quantifying nocturnal blood pressure dip. Normal nocturnal BP has been defined as 120/70mmHg based on population data (O'Brien et al 2003) or, based on cardiovascular outcome data, 110/70mmHg (Kikuya et al 2007). How these cut-offs are used in clinical practice are addressed in chapter 6.

Nocturnal dip was originally defined as a mean nocturnal systolic decrease of 10mmHg compared to daytime mean systolic pressure (O'Brien et al 1988). Over time, the accepted definition of dipping has become a nocturnal fall of more than 10% mean daytime pressure. This is not universally applied and neither are the methods of calculation. As most published literature on dipping uses a dip of >10% to define a dipper as a dichotomous variable, I have used this to try and be confluent with existing literature. However, other methods have advantages. Cumulative sums (cusums) are a statistical method for calculating diurnal variation in blood pressure independent of fixed time intervals (Stanton A et al 1992). Calculation of this type needs each individual blood pressure measurement taken over a 24-hour period, which is related to the mean, to realise the circadian pressure change. Unfortunately due to the retrospective nature of the analysis in this chapter, I could not access this information and had only the mean day and mean night blood pressure to use in analysis.

There is some controversy over nocturnal blood pressure dipping and adverse cardiovascular outcome. There is extensive evidence that lack of nocturnal blood

pressure dipping (nocturnal BP decline of <10% daytime average) is associated not only with increased left ventricular mass (Verdecchia et al 1990) and decline in renal function (Davidson et al 2006), but also increased risk of cardiovascular events in both population studies (Ohkubo et al 2002, Mancia et al 2006) and those specific to hypertensive cohorts (Verdecchia et al 1994, Staessen et al 1999, Clement et al 2003, Dolan et al 2005), with the possibility that this extends into the normotensive population (Ohkubo et al 2002). However, recent evidence has suggested that both daytime and night-time blood pressures are equally predictive of non-fatal cardiovascular events (e.g. MI and stroke) and nocturnal pressure is only superior in predicting fatal cardiovascular and total mortality (Boggia et al 2007, Conen et al 2008).

Treating nocturnal blood pressure dipping as a dichotomous variable, i.e. dipper or non-dipper, is problematic. A paradox exists between the poor reproducibility of dipping status (Mochizuki et al 1998, Omboni et al 1998, Manning et al 2000, Cuspidi et al 2004, Ben-Dov et al 2005) and the increased cardiovascular risk associated with non-dipping i.e. one would assume subjects with high cardiovascular risk are persistent non-dippers. How can this apparent paradox be resolved? Boggia *et al* (Boggia et al 2007) have demonstrated a continuous inverse relationship between nocturnal decline in blood pressure and cardiovascular risk. When nocturnal BP decline is expressed as a continuous variable, this data, as well as one previous small study (Chaves et al 2005), has demonstrated reasonable reproducibility. It is worth considering why this is the case.

Nocturnal blood pressure dip has a Normal distribution, evidenced by our data and others (Staessen et al 1997). If an arbitrary line is placed near the middle of a normal

distribution curve, which defines 'dipper' or 'non-dipper', subjects will move from one side to the other as a result of only a very small change in blood pressure. This is analogous to the imprecise reproducibility of classification of subjects as 'hypertensive' or 'normotensive' or any other physiological variable where we impose a dichotomisation on a continuous scale (Benediktsson et al 2004). Therefore, it is not surprising that given an arbitrary cut-off of 10% to define dipping, subjects will move categories, leading to the well-documented poor reproducibility of dipping status (Parati et al 2007). In describing an individual's nocturnal dip as a percentage of daytime pressure, this will be more stable over time, and, perhaps more valuable in terms of predicting cardiovascular risk.

There are limitations of any retrospective, observational analysis but these results do yield important findings in terms of reproducibility of nocturnal blood pressure dipping. The ABPM database at the Western General in Edinburgh is one of largest to be reported on and reflects "real life" rather than carefully controlled study conditions. The main strength of this study is the long time interval between ABPM assessments. No other studies have examined reproducibility of ABPM and dipping over such a long time course in patients free from pharmacological treatment. It would have been advantageous to confirm day night BP change by another method of analysis e.g. cusums however due to the limitations of the available data, this was not possible.

The majority of antihypertensive drugs are taken in the morning and the maximum effect occurs during the day. In the smaller section of subjects in whom ABPM was repeated after antihypertensive therapy is instituted, the mean nocturnal dip fell, probably due to



morning dosing. However, as the median absolute change in percentage nocturnal dip (4.4%) was not substantially different to those patients with 2 episodes of ABPM with no therapeutic intervention (3.8%), it could be concluded that antihypertensive drugs have no systematic effect on nocturnal dip. This does raise the interesting question as to whether or not this would still hold true if subjects split timings of medications or took all medications at night.

In conclusion, this analysis has demonstrated reproducibility of dipper / non-dipper classification consistent with the published literature. However, in the largest cohort of subjects examined to date, I have demonstrated that an individual's nocturnal blood pressure dip is essentially stable over time when expressed as a continuous variable, which would be more consistent with the published literature detailing an improved cardiovascular risk profile in "dippers". Reporting of nocturnal dip should be expressed as a continuous, rather than a dichotomous, variable as this is more clinically relevant in relation to quantifying cardiovascular risk.

## Chapter 4

### **The use of ambulatory blood pressure monitoring in primary care**

#### *Background*

It is widely recognised that hypertension is sub-optimally treated, with only 40-50% of hypertensive patients achieving blood pressure control ( $\leq 140/90$ mmHg) (NICE 2006, Scottish Health Survey 2003). As a result of sub-optimal treatment, hypertension is estimated to account for an “excess” 42,800 strokes and 82,000 ischaemic heart disease events per year (He *et al* 2003). In addition, evidence suggests that how quickly blood pressure is controlled is also important (Julius *et al* 2004). Accurate diagnosis and prompt treatment is therefore essential.

In April 2004, the new General Medical Services (nGMS) contract was implemented. In short, it provides remuneration for target achievement in a variety of clinical domains, with hypertension one such domain. This is further sub-divided into 5 sections with BP5 recording how many patients with documented hypertension are below a certain target ( $150/90$ mmHg). The results for all UK practices are documented in the Quality Outcomes Framework (QOF) and freely accessible. In Scotland this is through the information services division (ISD). Results from 2006-2007 suggested most practices in the UK achieved the 80% target of  $\leq 150/90$  (this figure excludes ‘excepted’ patients who do not comply with medication, or are otherwise unsuitable).

Ambulatory blood pressure monitoring (ABPM) can provide unequivocal evidence of hypertension without the need for repeated measures in primary care. British, European and American Societies of Hypertension (O’Brien *et al* 2005, Pickering *et al*

2005) have recommended ABPM to establish a 'true' diagnosis of hypertension, especially in the case of suspected "white coat hypertension" and resistant hypertension.

### ***Aim***

The principal aim of this study was to find out whether, if presented with an unequivocal hypertensive ABPM result, GPs would respond appropriately with drug therapy. Also, the proportion of patients on single, dual or more antihypertensive medications would indicate the scope for therapeutic intervention if control was suboptimal. Lastly, by examining patients before and after the implementation of the nGMS contract, one could speculate on the effectiveness of this rather costly change to primary care funding.

### ***Methods***

The principal driver behind the design of this study was the publication of the VALUE trial, which demonstrated if BP is controlled quickly after the diagnosis of hypertension, cardiovascular risk is significantly reduced (Julius *et al* 2004). The only readily accessible data available on BP control in hypertension comes from the QOF figures from ISD. However, there is no possible way to determine, from these results, the speed to control of hypertension. A large part of this rests on knowing when a diagnosis of hypertension has been given to each patient – is it a mean of blood pressure readings taken over months (if so, how many readings?) or when BP is over a certain level? Information in chapter 6 demonstrates not even British and European experts can agree on what level of blood pressure defines 'hypertension', despite guidelines published by them!

One way to more accurately define the point of diagnosis is the date of ABPM which shows unequivocal hypertension. Previous studies (based on advice regarding individual ABPM reports rather than absolute levels of BP), have demonstrated GPs commence antihypertensive medication in only 76% of cases when this is recommended (Richards *et al* 2004). This study (Richards *et al* 2004) did not have specific BP inclusion criteria but was simply based on whether or not GPs followed advice of the clinician who reported the ABPM. The decision to commence (or not) antihypertensive medication may have been influenced by the GP-patient interaction and their calculated cardiovascular risk, rather than absolute level of BP. In designing this study, the decision was made to “raise the bar” to a level where antihypertensive treatment should have been commenced, according to current and/or previous guidelines, irrespective of calculated cardiovascular risk. Therefore, the inclusion criteria of awake-time blood pressure on ABPM of >145/95mmHg was chosen on the [perhaps false] assumption that GPs recognise the average 10/5mmHg difference between OBP and ABPM and therefore this would represent a minimum OBP of 155/100mmHg. At this level, treatment would be mandated by all guidelines. Whilst hypertension guidelines may have changed over the time of this study with respect to the treatment of systolic pressure, a diastolic pressure of 100mmHg should always be treated (Williams *et al* 2004).

The hospital ABPM database was used to identify 400 never-treated, newly diagnosed hypertensive (mean awake BP>145/95mmHg) patients, equally divided pre and post nGMS contract. All were referred from primary care to confirm or refute a diagnosis of hypertension and therefore the date of ABPM was treated as the definitive diagnosis of

hypertension. Patients identified for pre-contract analysis had a diagnosis date between 1<sup>st</sup> January 2000 and 1<sup>st</sup> February 2002. Post contract analysis patients had a diagnosis date between April 2004 and March 2006. The subsequent management of hypertension in primary care was examined for the year following diagnosis.

The study included patients from 30 practices, managed by 130 GPs. Research nurses traced full primary care records of 191 pre-contract and 188 post-contract. Both paper and computer records were manually reviewed to obtain the time between diagnosis (ABPM) and the first subsequent GP visit; the “office” blood pressure at the first and final visit during the 12 months post diagnosis; the total number of GP visits and BP checks within the year following ABPM and the total number of anti-hypertensive agents per patient at one year. No patients were reviewed in a secondary care hypertension clinic.

As this was an evaluation of the impact of a current service, the chair of the local ethics board agreed formal ethical approval was not required.

### ***Statistics***

Blood pressure comparison within groups was calculated using the student's T-Test (Microsoft Excel, Microsoft),  $p < 0.05$  regarded as significant. Repeated measurement ANOVA (Graphpad Prism software) was used to calculate significance of treatment on mean blood pressure fall pre and post GMS contract. CHI squared was used to compare proportions of patients achieving nGMS targets pre and post contract.

## **Results**

Results at 1 year represent the last recorded 'office' blood pressure in the GP surgery within the year post diagnosis. Results are expressed as means  $\pm$  SD. The initial results describe all patients in terms of treatment or no treatment, which are then further subdivided into pre and post nGMS contract.

352 (93%) patients had BP results at one year. The mean office blood pressure fell from 155/91 ( $\pm$  17/11) mmHg to 147/86 ( $\pm$  16/11) mmHg,  $p < 0.001$ . A total of 58% were  $\leq 150/90$  mmHg and 36%  $\leq 140/90$  mmHg. Of the 352 patients, 287 (82%) were commenced on antihypertensive treatment.

### *Treatment versus no treatment*

Those commenced on antihypertensive therapy ( $n=287$ ) were significantly older (56 vs. 50,  $p < 0.001$ ) than those not on treatment ( $n=65$ ). The systolic ABP was the only significantly different blood pressure parameter at the start of the study (table 4.1). In the treated group, OBP fell significantly by 9/5mmHg and by a non-significant 2/1mmHg in the non-treated group.

Table 4.1.OBP and ABP at time of diagnosis of hypertension in subjects subsequently treated or not treated

		Treated	Non-treated
OBP	Systolic	155 (±17)	154 (±15)
	Diastolic	90 (±10)	91 (±11)
ABPM (awake)	Systolic	157 (±9)	153 (±7)§
	Diastolic	90 (±10)	92 (±8)

§p=0.006

***Monotherapy versus dual therapy at one year***

Those patients who ended up on dual therapy at one year had a significantly higher initial systolic pressure on ABPM and OBP, as well as diastolic OBP (table 4.2). Those on dual therapy had a mean of one more visit (n=9) and 2 more BP checks (n=7) within the year compared to those remaining on monotherapy.

Table 4.2. Baseline ABP & OBP in monotherapy & dual therapy groups

Initial BP		Monotherapy	Dual therapy
OBP	Systolic	153 (±17)	163 (±14)§
	Diastolic	89 (±10)	94 (±10)†
ABPM (awake)	Systolic	155 (±8)	160 (±11)§
	Diastolic	93 (±10)	95 (±11)

§=p<0.001, †=p=0.002

Subsequent results are subdivided into before and after implementation of the nGMS contract. Both groups had a median time of one month between ABPM and first GP visit (range 4-16 weeks).

### **Pre-nGMS**

Data at one year were obtained from 191 patients of whom 76% (n=143) were on anti-hypertensive agents, 18% (n=34) on no anti-hypertensive treatment and 7% (n=14) did not return within one year.

#### *Patients on Anti-hypertensive Medication*

After one year of treatment, office BP had fallen from 154/90mmHg to 148/86mmHg ( $p < 0.05$ ), 60% (n=84) achieved  $\leq 150/90$ mmHg and 17% (n=24) were  $< 140/90$ mmHg. Just over half (55%, n=106) were on mono-therapy, 18% (n=34) on dual therapy,  $< 1\%$  (n=3) on three or four agents. Table 4.3 demonstrates improvements in BP dependent on number of antihypertensive medications. Both mean ABPM and baseline office systolic blood pressure (for those on two agents) were higher than for those on one or no agents ( $p=0.002$ ). Patients attended on average 8 times (range 1-27) with a mean of 5 BP readings.

#### *Patients on no Treatment*

Mean office BP was no different from baseline to follow-up in the 34 untreated patients (153/92mmHg to 152/91mmHg). These patients attended an average of 5 times (range 1-21) but only had blood pressure checked twice,  $p < 0.001$  for total number of blood pressure checks compared with the treated group.



The treated patients were significantly older – 58 years ( $\pm 11$ ) versus 49 years ( $\pm 13$ ),  $p < 0.001$ .

## **Post nGMS**

Data at one year were obtained on 188 patients, of whom 77% ( $n=144$ ) were on anti-hypertensive agents, 16% ( $n=30$ ) were on no anti-hypertensive agents and 7% ( $n=14$ ) did not return within one year.

The BP5 QOF data from the participating practices were extracted for the year April 2006 to March 2007, the timeframe during most of the post nGMS section of the study. According to ISD, the target BP was achieved in 81% of patients.

### *Patients on Anti-hypertensive Medication*

At one year of treatment office BP fell from 156/91mmHg to 144/85mmg ( $p < 0.001$ ), 66% ( $n=95$ ) achieved an OBP  $\leq 150/90$  mmHg and 39% ( $n=44$ )  $< 140/90$  mmHg. Monotherapy was used in 60% ( $n=112$ ), dual therapy in 15% ( $n=29$ ) and  $< 1\%$  on either triple therapy or four anti-hypertensive agents. Baseline office BP was significantly higher in those on dual therapy compared to monotherapy (systolic  $p=0.003$ ). All other baseline comparisons, office or ABPM, were non significant. Table 4.3 outlines differences in control depending on number of anti-hypertensive medications.

Patients attended on average 8 times (range 1-26) with a mean of 5 BP readings.

### *Those on no Treatment*

Office BP was no different (154/88mmHg to 152/87mmHg) after one year of follow-up in the 30 patients on no treatment (table 4.3). Patients attended a mean of five times

(range 1-13) with only two BP readings on average. This was significantly less than the treated population,  $p < 0.001$ .

Unlike the pre-GMS patients there was only a trend towards older patients being commenced on antihypertensive treatment – treated – age 54 ( $\pm 11$ ) and non treated age 50 ( $\pm 17$ ),  $p = 0.07$ .

### **Pre and Post contract**

In the 12 months following the diagnosis of hypertension pre contract, mean office BP decline was 5/3 mmHg and post contract, mean office BP decline was 10/5 mmHg,  $p < 0.001$ . However, comparing proportions achieving nGMS targets pre (60%) and post (66%) contract implementation, this was not significant,  $p = 0.62$ .

Table 4.3 – BP at diagnosis and one year post diagnosis for all patients, both pre nGMS and post nGMS contract

	ABPM			1 <sup>st</sup> GP BP		12 month GP BP		OBP fall	Significance		% reaching target	
	Patients	Sys	Dia	Sys	Dia	Sys	Dia		Sys	dia	≤ 150/90	≤ 140/90
Pre GMS	177	157(9)	93(9)	154(17)	90(10)	149(14)	87(10)	5/3	<0.001	<0.001	53	29
no therapy	34	153(6)	92(7)	153(14)	92(8)	152(17)	87(13)	1/5	0.7	0.1	26	12
monotherapy	106	156(8)	92(10)	152(17)	88(10)	147(15)	85(10)	5/3	0.02	0.006	62	36
dual therapy	34	162(12)	95(10)	162(14)	93(11)	150(15)	88(11)	12/5	<0.001	<0.001	53	27
Post GMS	174	155(7)	93(10)	156(17)	91(11)	146(17)	86(11)	10/5	<0.001	<0.001	63	41
no therapy	30	154(7)	91(9)	154(16)	88(14)	152(17)	87(13)	2/1	0.3	0.3	50	23
monotherapy	112	155(9)	93(10)	153(17)	90(10)	145(16)	85(10)	8/5	<0.001	<0.001	63	45
dual therapy	29	158(10)	94(12)	163(14)	94(10)	140(15)	82(10)	23/12	<0.001	<0.001	76	50

Nb. Those patients on 3 or 4 antihypertensive agents are not included in the results summary table.

## ***Discussion***

The aim of this audit was to define what proportion of patients achieved blood pressure control at one-year following an unequivocal diagnosis of hypertension as defined by ABPM. If this was found to be sub-optimal, there would be a clear indication to reconsider how hypertension is managed in primary care. In addition, examining BP control pre and post implementation of the nGMS contract could allow a degree of speculation as to whether or not the contract has made any difference to the management of hypertension in primary care. I accept this group of patients may not be representative of the general hypertensive population and there is no control group i.e. one without ABPM for comparison. However, for the reasons outlined in the methods section, it is difficult to see how such a control group could have been identified.

The results of the audit are clear: there is no significant change in the number of patients achieving <150/90mmHg after the implementation of the contract and there is a 15% discrepancy between my findings and the quoted figures from ISD, with respect to the percentage of patients achieving <150/90mmHg. Also, with no apparent change in treatment intensity, measured office blood pressure is significantly lower (by 5/2 mmHg,  $p<0.001$ ) in the post nGMS group.

There are several possible explanations for the large discrepancy between my figures and the figures from ISD with respect to the number of patients achieving target BP.

The first is related to timing of OBP measurements. The results in QOF are for data collected April 2006 to March 2007. If, for example, patient X has a date of diagnosis of hypertension as defined by ABPM in January 2007, and the first OBP from the GP in

March 2007 was <150/90mmHg, they were controlled according to the QOF data. However, patient X will have been followed until January 2008. If subsequent OBP at this stage was >150/90mmHg, they were 'uncontrolled' on my data. This illustrates the problem of using only single office readings, where the coefficient of variation can be as high as 12% (Warren *et al* 2008).

The second possibility is that the population referred for ABPM is somehow different to the routine primary care population. There is evidence from unpublished work that general practitioners refer patients for ABPM mainly for diagnosing of white coat and resistant hypertension. This does not apply to the current study – due to the inclusion criteria, none of our patients had white coat hypertension. Also, all our patients were treatment naive and resistant hypertension is generally defined as hypertension despite 3 or 4 antihypertensive agents. It may be that patients referred for ABPM are those who are reluctant to receive antihypertensive therapy. GPs are then using ABPM as additional evidence, perhaps to try to convince this relatively young population to accept treatment. The evidence behind this assumption is that 64 subjects (17%) were not commenced on antihypertensive treatment and 28 subjects (7%) did not return to their GP within a year of the ABPM. In addition, 75% of the treated group remained on monotherapy despite sub-optimal OBP. This may reflect physician inertia or patients not willing to escalate therapy.

It may be that GPs are falsely reassured by the ABPM if they do not understand the 10/5mmHg difference between mean awake BP on ABPM and OBP. This is not clearly documented on the ABPM report form generated by the system. Therefore GPs may have taken the ABPM reading as equivalent to OBP and, in the absence of other

on a single antihypertensive drug. Therefore, why institute a method of assessment, which is expensive, when it does not affect decision making? Perhaps future guidance from both British and European societies should be more succinct and dogmatic i.e. hypertension diagnosed by ABPM leaves no dubiety over the diagnosis and, in keeping with European guidelines, all patients with grade 2 hypertension should be started on dual therapy at point of diagnosis (Mancia *et al* 2007). In relation to this study, this would have meant all patients starting dual therapy following diagnosis. Further qualitative research is required to try and delineate why antihypertensive treatment was not started in some or escalated despite an unequivocal diagnosis and subsequent office blood pressures that remained above target.

## Chapter 5

### **The Use of Ambulatory Blood Pressure Monitoring in Secondary Care**

#### *Background*

The excess premature vascular disease morbidity and mortality associated with diabetes is well recognised (Huxley et al 2006). This is secondary to the atherogenic milieu of dyslipidaemia, hypertension and hyperglycaemia. As a result, type 2 diabetes has been estimated to “age” the vasculature by 15 years (Booth et al 2006).

There is consistent evidence that vascular risk can be substantially decreased by treatment of blood pressure (Turner et al 1998, Hansson et al 1998) and dyslipidaemia (MRC/BHF 2003, Colhoun et al 2006). Despite this knowledge, blood pressure is not controlled in the majority of patients with type 2 diabetes and suboptimal numbers of patients are on lipid lowering therapy (Eliasson et al 2005).

Failure to achieve targets using these therapies is multi-factorial. Many patients with diabetes need multiple therapy for hypertension as well as oral hypoglycaemic agents and lipid lowering therapy (Graede et al 2003). Adherence to medication is one important factor particularly in conditions such as diabetes where there are few symptoms. Adherence to oral hypoglycaemic monotherapy for diabetes, as one example, is known to be poor with only 30% of patients having >90% drug adherence, this figure falls dramatically as the number of medications increases (Donnan et al 2003). There are similar data for the treatment of hypertension (Halpern et al 2006).

Measurement of blood pressure is also problematic. Patients should be resting in a seated position for at least 5 minutes. The back and arm should be supported, all clothing that covers the location of the cuff removed and have the mid point of the cuff at the level of the right atrium (Pickering et al 2005). This is often difficult to achieve in busy diabetes clinics. Using 24-hour ambulatory blood pressure monitoring, it has been demonstrated that clinic blood pressure measurements overestimate blood pressure by 14-16/4-6 mmHg (Dawes et al 2006, Dolan et al 2005). Recent research has demonstrated that specifically in relation to diabetes, ABPM is important as there appears to be a much higher incidence of masked hypertension and nocturnal non-dipping, both proven to further increase cardiovascular risk in an already high risk population (Palmas et al 2009). Awareness of this may lead to reluctance to recommend treatment, as a “true” blood pressure may not be measured during the consultation.

To address these issues, a pharmacist-led clinic for people with diabetes identified as having particularly high cardiovascular risk was introduced as a service development. However, it is not clear whether a clinic of this type would lead to a sustained reduction in the parameters associated with increased cardiovascular risk, over and above preceding clinic based “usual care”.

### ***Aims***

There were 2 main aims for this study: Firstly, is the pharmacist-led clinic effective at reducing cardiovascular risk and secondly, is this benefit sustained after discharge?



## **Methods**

Patients were referred to the pharmacist-led diabetes cardiovascular risk clinic from the general diabetes clinic at the Western General Hospital, Edinburgh. Referral criteria were broad, but the clinic was primarily aimed at people whose cardiovascular targets (blood pressure and/or lipids) were not being met and who were deemed to be at high cardiovascular risk (typically people with established cardiovascular disease and/or chronic kidney disease). At the time of the study, 184 patients had been referred to the cardiovascular risk clinic, with 82 patients discharged. The inclusion criteria for the study were that patients had to have been through the cardiovascular risk clinic, have been discharged for at least six months and had an ABPM on discharge from the clinic (n=40). Ideally, follow up should have been for a year or more but due to the nature of this service development and the time of study, no patients had been discharged from the cardiovascular risk clinic for a year or more.

Ambulatory blood pressure data at clinic entry was present in 30% of the study population. This is because the pharmacy led clinic was part of a service development plan and as such protocols have developed over time.

“Usual care” is attendance at the hospital diabetes clinic (organised) in conjunction with primary care visits as initiated by the patient. The study group experienced usual care plus extra visits to the pharmacy - led clinic as initiated by the secondary care team.

### *Initial consultation with the pharmacist*

Hypertension was confirmed using the average of 3 measurements taken after 5-10 minutes rest using a mercury sphygmomanometer (measurements taken by the same

cardiovascular risks, simply chosen to continue to monitor what they perceive as grade 1 hypertension.

Lastly, it is well recognised that routine blood pressure measurement is open to all forms of bias – terminal digit preference, intra and inter-observer bias, white coat effect and even the accuracy of the devices that are used. It is unclear if certain aspects of these biases are more exaggerated in the context of an incentivised health care service. It is difficult to draw this conclusion from the data presented in this chapter. To consider this as a possibility, different outcomes would need to be assessed where there is no possible biases at point of testing e.g. mean HbA1c levels, lipid levels etc. If this sort of data had been collected, more inference could perhaps have been drawn on bias in incentivized health care.

Of interest is the discrepancy between the number of GP visits and the number of blood pressure checks. All patients included in this study had unequivocal hypertension, and, in both groups, there was room for further therapeutic intervention, as evidenced by the poor control rates. On average, blood pressure was only checked during 50% of visits.

In conclusion, even with unequivocal evidence of hypertension as demonstrated by ABPM, blood pressure appears to be less well controlled in this group than in the general population. Advocates of ABPM have proposed that assessment and management of hypertension in primary care is impossible without using ABPM (O'Brien 2008), not without a heavy weight of evidence to support their argument. However, from a pragmatic point of view, hypertension confirmed by ABPM did not appear to influence therapeutic aggressiveness, as evidenced by the majority staying

pharmacist for all patients). Medications were confirmed and drug adherence assessed. Renal function and urinary albumin/creatinine ratio were measured. Lipid results were available from their preceding diabetes clinic visit.

The benefits of taking their antihypertensive, lipid lowering and antiplatelet medications and possible side-effects were explained. The need for methods to improve adherence, e.g. use of medidose devices was also assessed.

The pharmacist discussed each case with the consultant responsible for the clinic before making written treatment recommendations to GPs. Medications were altered via the patients' GPs in accordance with a treatment protocol based on British Hypertension Society guidelines (Williams et al 2004). The stepwise treatment plan for antihypertensive therapy is outlined in figure 5.1. Macrovascular disease (defined as documented evidence of ischaemic heart disease or cerebrovascular disease) includes those patients with diabetic nephropathy (albumin/creatinine ratio >30mg/mmol) or microalbuminuria (albumin/creatinine ratio >2.5mg/mmol in males and >3.5mg/mmol in females).

Lipid lowering therapy was used in all patients > 40 years old (type 1 and type 2) with a total cholesterol > 3.5mmol/l (as they had significant hypertension) and patients < 40 years old with established nephropathy or macrovascular disease. Antiplatelet therapy was used in patients > 50 years old with a 20 % 10 year risk of vascular disease or <50 years old with nephropathy or macrovascular disease. This was commenced when blood pressure was <160/90 mmHg.

### *Follow up*

Patients were reviewed approximately every 6 weeks (a mean number of 4 visits) until target BP was achieved (<140/80 mmHg or <130/80 mmHg in patients with macrovascular or microvascular complications), or no further improvement could reasonably be obtained. The target BP was based on guidance from the Scottish Intercollegiate Guideline Network - SIGN 55, Management of diabetes. Since this study completed, this has been superseded by SIGN 116 which recommends a target BP of <130/80mmHg.

The pharmacist also frequently contacted the patients' community pharmacist and/or General Practice to check patient compliance with their medications and to arrange for provision of compliance-aids.

Healthy lifestyle advice including weight reduction, smoking cessation, reduction in alcohol consumption and increasing exercise levels was given as indicated.

40 patients fulfilled the inclusion criteria. Of these, 34 patients agreed to take part and had a further ABPM at least six months post discharge.

The repeat clinic blood pressure was a single measurement taken with oscillometric device after the patient had been sitting at rest for 5 minutes, immediately prior to 24 hour ambulatory blood pressure measurement (ABPM) commencing. ABPM was performed using a Spacelabs 90207 with blood pressure measurement every thirty

minutes during day and night, defined by patient diary. A mean awake blood pressure can be calculated from the patient diary.

The study was approved by the local ethics committee.

### **Statistics**

Blood pressure data are expressed as means,  $\pm$  standard deviation. Two tailed T-test was used to compare data with  $p < 0.05$  considered statistically significant.

### **Results**

34 patients participated - all had type 2 diabetes, 47% with established cardiovascular disease and 34 % with nephropathy as defined by an elevated albumin/creatinine ratio (not mutually exclusive). With regards diabetes control, 7 patients were on diet only, 22 treated with oral hypoglycaemics alone, 2 treated with combination oral hypoglycaemics / insulin and 3 on insulin only. The mean age was 66 ( $\pm 10$ ), 59 % male. Mean BMI 32 ( $\pm 5$ ) and 15% current smokers. The mean number of antihypertensive drugs at clinic entry was 2.82 ( $\pm 1.05$ ). Mean referral blood pressure was 172/87  $\pm$  18/11 mmHg.

### *Therapeutic intervention*

Table 5.1 demonstrates the number of patients on each main subclass of antihypertensive, lipid lowering and antiplatelet drugs at clinic entry, discharge and follow up.

The number of additional antihypertensive drugs increased by 1 in 9 patients, 2 in 6 patients and 3 in 3 patients. 10 patients had no change in total number of

antihypertensive medications but had dose increases and 5 patients had no increase in total number of medications or dose.

Table 5.1 Medications of study population (n=34) at entry and discharge from the cardiovascular risk clinic, and at six month follow up

	Initial visit	Discharge	Follow up
Diuretic	26	32	31
BB	19	24	23
ACEI	19	19	18
AlI RA	7	10	9
CCB	15	24	21
AB	4	10	12
Others	2	3	1
LL	22	27	28
AP	25	29	29

BB=Beta blocker, ACEI=angiotensin converting enzyme inhibitor, AlIRA=angiotensin II receptor antagonist, CCB=calcium channel blocker, AB=alpha blocker, others=other antihypertensive drug classes, LL=lipid lowering agent, AP=antiplatelet.

Medication change during clinic attendance

The mean number of antihypertensive drugs per patient increased from 2.82 ( $\pm$  1.05) to 3.67 ( $\pm$  1.03). At 6 months follow up, this remained unchanged at 3.48 ( $\pm$  1.12).

Lipid lowering therapy was commenced in 5 patients and doses increased or the statin changed in 9 patients.

#### *Clinic Blood Pressure*

Mean referral blood pressure (n=34) was  $172/87 \pm 18/12$  mmHg and  $167/83 \pm 16/10$  mmHg at clinic entry ( $p=0.035$ ). Blood pressure on discharge was  $144/73 \pm 15/7$  mmHg on discharge ( $P<0.001$ ). At least six months post discharge, clinic blood pressure unchanged –  $136/69 \pm 17/11$  mmHg ( $p>0.05$ ).

#### *24-hour ambulatory blood pressure at clinic discharge and follow up*

All patients (n=34) had ABPM at discharge and follow up. Mean awake blood pressure was  $131/67 \pm 9/4$  mmHg at discharge, and  $129/67 \pm 11/7$  mmHg six months post discharge ( $p>0.05$ ).

#### Ambulatory blood pressure data at clinic entry, discharge and follow up

30 % (11 patients of the total study population, n=34) had ABPM at clinic entry, discharge and follow up (figure 5.2).

27% had established cardiovascular disease and 18 % had nephropathy as defined by an elevated albumin/creatinine ratio. The mean age was 64 ( $\pm 10$ ), 72 % male. Mean BMI 29 ( $\pm 3$ ) and 18% current smokers. The mean number of antihypertensive drugs at clinic entry was 2.8 ( $\pm 1.0$ ).

Mean referral blood pressure was  $183/91 \pm 20/12$  mmHg and  $176/82 \pm 19/9$  mmHg at clinic entry ( $p>0.05$  for systolic and diastolic). On discharge, clinic blood pressure was

144/73  $\pm$  20/8 mmHg ( $p=0.0004$  for systolic BP and  $p=0.004$  for diastolic BP compared with clinic entry) and 135/69  $\pm$  13/12 mmHg at follow up ( $p>0.05$  systolic and diastolic BP).

ABPM mean awake blood pressure at clinic entry was 148/79  $\pm$  10/6 mmHg, 135/72  $\pm$  9/7 mmHg on discharge ( $p<0.001$  systolic and diastolic BP) and 129/67  $\pm$  14/7 at six month follow up ( $p>0.05$  systolic and diastolic BP).

### Lipids

Total cholesterol was 4.46  $\pm$  0.90 mmol/l at referral and fell to 4.02  $\pm$  0.72 mmol/l ( $p = 0.002$ ) at discharge and 3.91  $\pm$  0.91 mmol/l at six months ( $p=0.38$  compared to clinic discharge).

### **Discussion**

For those clinicians involved on a daily basis in the care of patients with type 2 diabetes, the problem of controlling cardiovascular risk factors is very familiar. Blood pressure is difficult to control in the longer term. This study examined a group of patients who had already received traditional diabetes care in an outpatient department but continued to have poorly controlled blood pressure within this system.

The aim of the study was to answer 2 questions – is the pharmacist-delivered clinic effective in reducing blood pressure and is this effect sustained after discharge?

The question of whether or not the effect is sustained is especially important given the recent 10 year follow up results of the UKPDS. This demonstrated that tight glycaemic



control after a new diagnosis of diabetes has a lasting effect on both macrovascular and microvascular complications, even if subsequent control is suboptimal (Holman et al 2008a). This was similar to findings from the EDIC study, a follow up of patients originally enrolled in the DCCT trial. Therefore, there appears to be an element of “metabolic memory” for glycaemic control. However, this was not the case for blood pressure control and persisting BP control is needed to improve outcome from cardiovascular disease (Holman R et al 2008b).

It is worth noting that there is no pressor effect of entering the pharmacy led clinic i.e. no significant difference between blood pressure at referral and clinic entry. Therefore, improvements in blood pressure were real and not simply regressing to the mean. Whilst the reductions in clinic blood pressures look impressive, the true answer lies in the ABPM data. The ABPM group is representative of the clinic with no statistically significant difference in blood pressure at referral or clinic entry. ABPM is devoid of placebo effect, white coat effect, observer bias and “evens out” the natural variability of blood pressure. Although the number of patients with ABPM at clinic entry, exit and discharge only made up 30 %, their results were statistically significant. They clearly demonstrated the clinic is effective in lowering blood pressure by an average of 13/9 mmHg.

This reduction was sustained in all patients who had attended the clinic, as demonstrated by no significant change in ABPM mean awake blood pressures between discharge and follow up.

Total cholesterol also decreased significantly and remained lower at follow up. This is secondary to a combination of increased prescription of lipid lowering agents (table 5.1) and likely increased patient compliance.

The main flaw in the methodology of this study was lack of a control group. Without intervention, a matched control group should have undergone ABPM at the same time intervals. It is not clear how much of the observed fall in BP during the clinic and in follow up was a result of improved adherence to antihypertensive medication already prescribed. The presence of a control group would have answered this question. This was not done as the first section of the study (to assess the BP decline in patients from clinic entry to discharge) was done retrospectively.

The success of this intervention could be due to a number of reasons. There was an increase of antihypertensive therapy. Patients received, on average, extra 0.75 antihypertensive medications. Given the true fall in blood pressure was 13/9 mmHg, the fall in blood pressure during clinic attendance may not have been just due to the increased prescription of medication.

The key to the success of the pharmacist led clinic was the pharmacist themselves. They had enough time for frequent visits for assessment, repeated education on the importance of antihypertensive medication and therefore encouraging compliance with existing therapy. In addition, they are more likely to be didactic in following protocols, as is commonly seen in clinical situations where patient management is principally governed by paramedical staff e.g. nurses and pharmacists. This will have led to escalation of therapy and improvement of blood pressure. Although not addressed

specifically, the improvements achieved in cardiovascular and cerebrovascular risk are likely to be cost effective, saving up to £ 35,000 per cardiovascular event avoided (Lowey et al 2007).

The initial blood pressure decline may not have been sustained when follow-up was less intense. However, ABPM confirmed blood pressure had sustained improvement from discharge to follow up.

During this period of time, patients would have had a maximum of one diabetes clinic visit but we do not have data on visits to a primary care physician. Whilst this study was carried out in secondary care, the patient population is identical to those who are looked after in primary care. Within the region (Lothian, Scotland) that this study population serves, there is already progress in setting up an identical service based in primary care. Given the greater numbers of diabetic patients served by primary care, there is scope for huge improvements in morbidity and mortality, not to mention the cost-saving potential if this was to be implemented throughout primary care.

This study emphasises that sustained reductions in vascular risk can be achieved in patients who have previously been believed to be resistant to intervention. This intervention is quite intense with regular (1 visit every six weeks) visits but the frequent visits may not be required for a very long period. With the greater numbers of patients who develop diabetes there is a need to involve more staff in improving care. Pharmacists, with their expert knowledge of drugs are one group that can contribute to diabetes care in this manner. Increasing the focus of care on those at highest risk is likely to provide the greatest benefit to our patients. This service redesign has produced

a sustained improvement in care and is likely to reduce longer-term complications and vascular disease.

Figure 5.1 Medication titration protocol for pharmacist led cardiovascular risk clinic

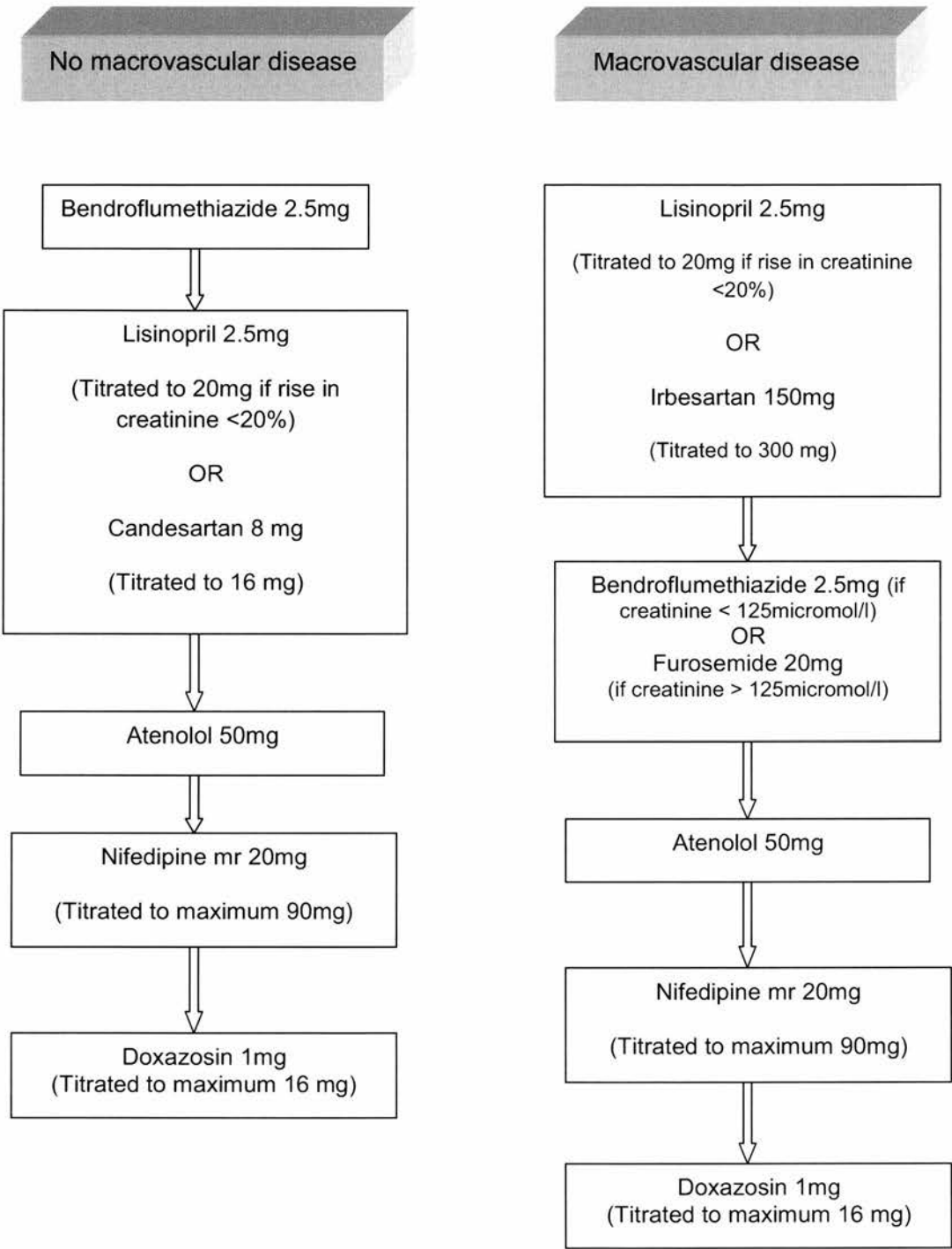
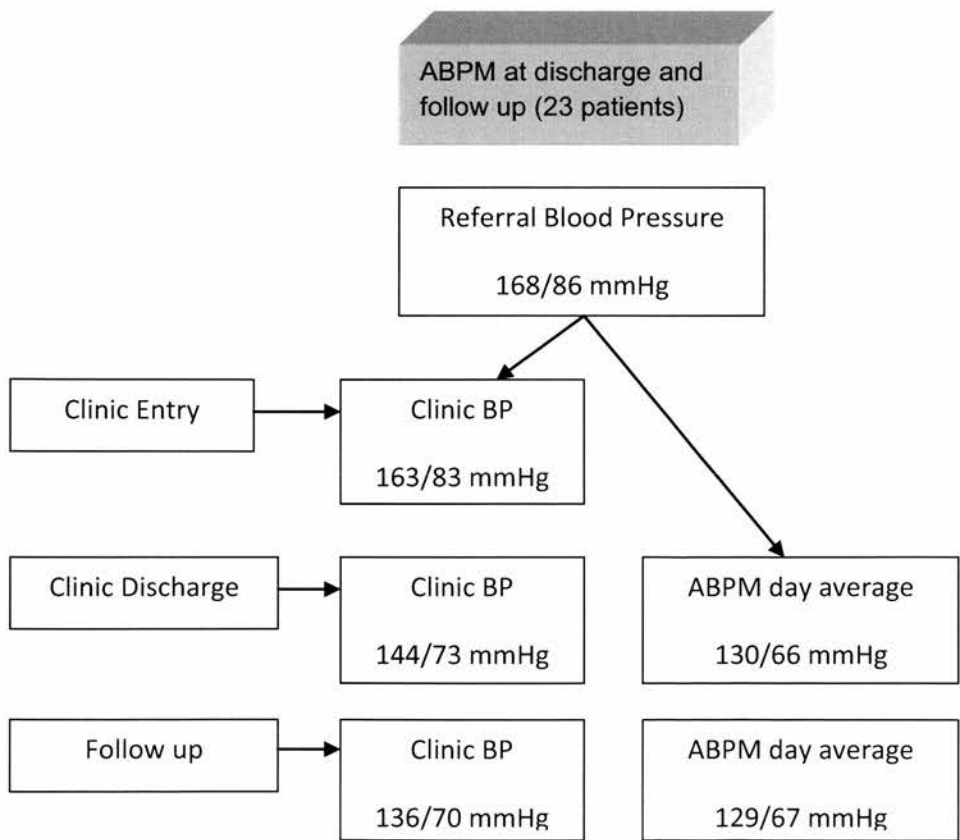
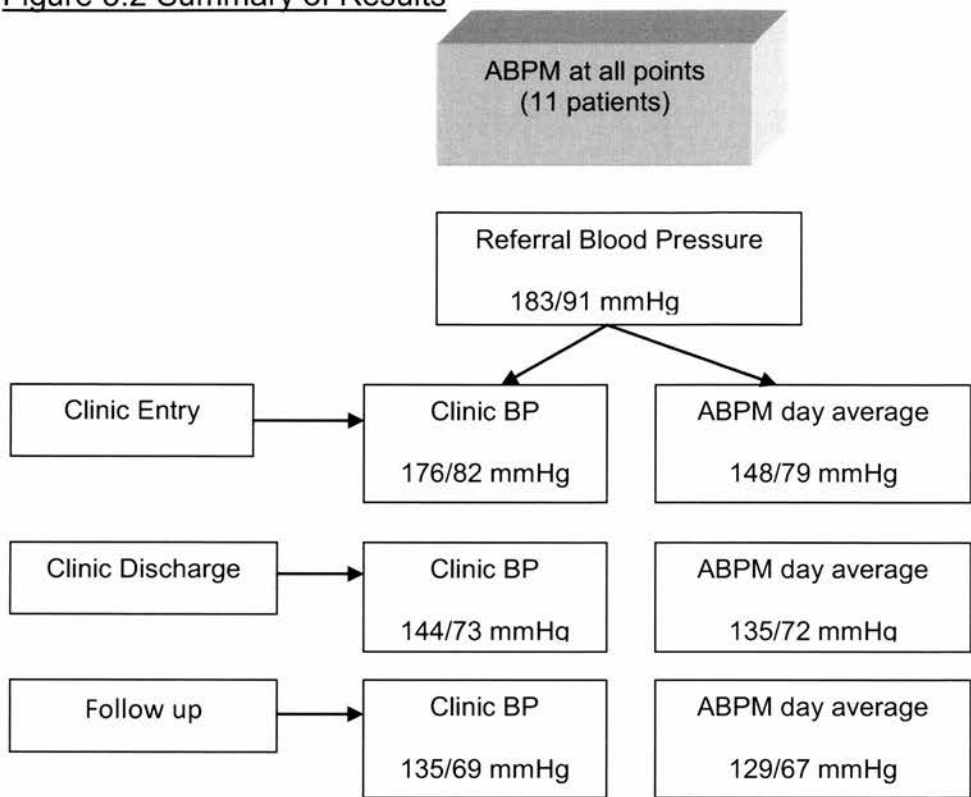


Figure 5.2 Summary of Results



## Chapter 6

### **How consistent are experts in reporting and interpreting ABPM?**

#### *Background*

Hypertension can be defined either by office blood pressure readings or ambulatory blood pressure. Whilst there is little debate over the former, the latter definition is less clear. ABPM is recommended by a host of national and international guidelines (McGrath 2002, Williams *et al* 2004, O'Brien *et al* 2005, Pickering *et al* 2005) but definition of hypertension on ABPM is not as clear cut. The definition of hypertension on ambulatory BP measurement was originally based on observational data from the PAMELA study, where those above the 95<sup>th</sup> centile were defined as hypertensive: awake BP  $\geq 135/85$  mmHg, nocturnal BP  $\geq 120/70$  mmHg or 24 hour BP  $\geq 130/80$  mmHg (Mancia *et al* 1995). This had been accepted by the British, European and American Societies of Hypertension. However, more recently the IDACO investigators have suggested these thresholds be redrawn to  $\geq 140/80$ mmHg,  $\geq 110/70$ mmHg and  $\geq 125/75$ mmHg for awake, nocturnal and 24hour blood pressures respectively, based on cardiovascular outcomes and ABPM data for > 7000 patients (Kikuya 2007). In addition, given the accepted average difference between office and out of office BP is 10/5mmHg (Williams *et al* 2004) and, if the definition of hypertension based on office BP is  $\geq 140/90$  mmHg (Chobanian *et al* 2003), then should this equate to an awake time average of  $\geq 130/85$ mmHg? Perhaps as a result of varying definitions and in the absence of official guidance, it is unclear how ABPM is used in practice or, indeed, whether there is any uniformity in its use, either between or within centres.

As discussed in chapter 2, all “direct access” ABPM reports (requests directly from primary care) are reported by a single clinician and recommendations on treatment are

appended prior to the report being returned to the requesting GP. The following studies were designed following the chance repeat reporting of an ABPM, with different advice given on each occasion.

### ***Hypothesis***

One advantage of ABPM is that it removes observer bias and inter-observer variability. This is reintroduced when relying on human interpretation of ABPM. The aim of these studies was to examine the intra- and inter-observer variability of interpretation of ABPM, treatment decisions based on ABPM and comparison of expert opinion with a computer interpretation.

### **Study 1 – Therapeutic decision making based on ABPM within the cardiovascular risk clinic of the Western General Hospital**

#### ***Methods***

252 ABPM reports were randomly selected from an 18-month period. All patient identifiable data and original recommendations were removed. They were distributed to the original clinician, 2 senior nurses, 2 registrars and 4 consultants running the cardiovascular risk clinic at the Western General Hospital.

#### ***Statistics***

Within observer agreement is expressed as a percentage. Inter-observer agreement is expressed as complete agreement between all observers and agreement with the most frequently returned answer i.e. the modal response.



## ***Results***

The within-observer concordance was 94.4%.

### ***Inter-observer consistency***

Complete concordance occurred in 5 %. Agreement with the modal answer varied from 58-79 % within consultants, 73 % for registrars and 88-92 % within nurses.

### ***Comment***

The single clinician involved in the service on a day-to-day basis demonstrated high reproducibility. When each ABPM was originally reported, there may have been supplementary information included as free text from the GP referral e.g. family history, smoking status. However, this was not included when the reports were distributed to all participants of the study. It is unlikely this made any significant difference otherwise there would not have been such a high level of within-observer concordance for the original reporter.

In the real life setting, the reporting clinician generally only suggests one of three options: treat / increase treatment, don't treat or repeat in 2-5 years. However, within the study, many more options were available to the respondents: (1) treat (2) don't treat (3) increase treatment (4) decrease treatment (5) more information needed (6) repeat after one year (7) stop treatment. Many participants felt uncomfortable simply stating "treat" or "don't treat" without more information e.g. smoking history, presence or absence of diabetes, history of cardiovascular disease etc or their response would not make sense

e.g. their answer would say 'don't treat' when the subject was already on treatment (all medications were included on the ABPM reports reviewed). It was unclear whether they meant treatment should be stopped, treatment should not have been started or treatment should be decreased. This undoubtedly contributed to the lack of agreement in reporting but the degree of disparity is surprising. If the options had been more restricted, greater concordance may have been obvious. However, this does not reflect real life.

Study 2 – Diagnosis and therapeutic decision making within members of the European Society for Hypertension Working Group on BP measurement.

**Methods**

A questionnaire was circulated to 21 members of the ESH working group asking for thresholds for instituting treatment, treatment targets and a variety of clinical scenarios (figure 6.1), asking for a treatment decision.

**Results**

Only 12 (57%) participated. Seven used ABPM for low-risk patients only, two for low risk plus those with target organ damage and three used ABPM for all patients. The modal response for awake ambulatory pressure for initiating drug therapy was 135/85 mmHg (range 130-145/80-95mmHg).

Seven used sleep systolic BP for drug initiation but again the threshold varied, ranging from 120 to 135 mmHg.

All used ABPM for the long-term management of patients with hypertension, eight (66%) using the same thresholds for control as for treatment introduction. Three used slightly lower target thresholds and one described a totally different set of thresholds for long-term management. For the 16 scenarios described in Fig. 1, there was complete concordance of recommendations in only two – patients 6 & 8 (see Fig. 6.1).

Figure 6.1. Clinical Scenarios given to the members of the ESH working group on blood pressure measurement – Does ABPM help and how?

Sex	Age	Office BP	FH	CVD/TOD	DM	Smoker	Chol/HDL ratio	Awake ABP	Sleep ABP	Treat (Y)
M	32	158/98	Y	N	N	N	4.5	140/89	116/69	8
M	64	148/90	N	MI	N	N	5.8	125/70	114/67	8
F	45	168/100	N	N	N	N	3.8	134/83	118/64	2
M	40	146/87	Y	N	N	N	4.1	136/88	124/68	4
M	82	178/88	N	LVH	N	N	5.9	132/66	120/50	7
F	73	140/90	N	N	N	Y	3.8	128/78	114/64	0
F	30	168/104	N	N	N	N	3.6	140/90	129/81	8
M	58	152/100	N	MA	N	N	4.3	132/87	145/80	12
M	38	170/110	Y	N	N	Y	3.1	142/86	122/75	10
M	46	156/94	N	N	N	N	4.4	134/78	140/80	6
F	33	162/100	Y	N	N	Y	5.0	138/84	120/78	6
M	38	140/90	N	N	N	Y	5.6	140/90	118/78	9
F	76	162/106	N	CVA	N	N	6.0	128/65	108/59	7
F	66	148/88	N	N	Y	N	4.7	132/83	122/75	7
M	37	139/88	N	N	N	N	4.6	145/89	128/78	6
F	80	188/87	N	PVD	N	N	5.4	138/89	119/77	10

Observers were asked to assume the office BP was the mean of at least two visits and all patients had normal renal function. DM = diabetes, FH = first degree relative with heart attack or stroke aged < 60. MI = myocardial infarction, LVH = left ventricular hypertrophy, MA = microalbuminuria, CVA = stroke and PVD = peripheral vascular disease.

Study 3 – Consistency of diagnoses and therapeutic decision making within members of the British Hypertension Society.

**Methods**

The questionnaire used in study 2 was expanded (appendix 6.1) and circulated to all members of the British Hypertension Society (approx.220), again asking for thresholds for instituting treatment and treatment targets. The clinical scenarios asking for a treatment decision were expanded, including 8 of the original scenarios.

There were 39 respondents, consisting of 29 senior hospital physicians, 4 senior primary care physicians, 4 senior nurses and 2 junior hospital physicians.

**Results**

ABPM is most commonly used in young patients and those with variability in office BP and least often in those with target organ damage. Average daytime blood pressure is most likely to influence response (84%, compared to 24 hour average BP – 21%) – Tables 6.1 & 6.2 respectively.

**Table 6.1.** Who are assessed by ABPM prior to commencing therapy?

	Almost always	Often	Rarely
Variable OBP	18	14	7
Elderly	10	6	23
Young and low risk	19	5	14
Target organ damage	10	1	26

**Table 6.2.** Which value most influences your response?

	Almost always	Often	Rarely
Mean awake BP	32	7	0
Mean sleep BP	9	9	21
24 hour mean BP	7	5	26

ABPM is rarely used to ascertain target BP has been reached but is used to monitor therapy in those who appear to be drug resistant or have white coat effect – table 6.3.

Self blood pressure monitoring is not used as frequently (table 6.4) and the respondents had different thresholds compared to ABPM.

**Table 6.3.** Which patients are assessed by ABPM during treatment?

	Almost always	Often	rarely
Variable OBP	11	12	15
'drug-resistant'	16	12	11
'white-coat' response	22	12	5
confirming target BP	4	6	27

**Table 6.4.** Which patients are assessed by SBPM?

	Almost always	Often	Rarely
For diagnosis	2	11	24
Monitoring treatment	2	13	22

Blood pressure thresholds (modal response)

To **commence** antihypertensive medication

- Awake blood pressure 140/90 mmHg (38 respondents)
- Nocturnal blood pressure 140/80 mmHg (20 respondents)
- 24 hour average 135/85 mmHg (17 respondents)

**Successful** treatment defined as

- Awake blood pressure 130/80 mmHg (37 respondents)
- Nocturnal blood pressure 120/80 mmHg (21 respondents)
- 24 hour average 130/80 mmHg (18 respondents)

**SBPM threshold** for treatment 150/90 mmHg (31 respondents)

With respect to the scenarios, agreement varied with an average of 50-60% of respondents agreeing for each scenario. The same was true for whether or not ABPM was helpful in clinical decision making.

### ***Comment***

Once again the degree of disparity that existed amongst hypertension experts over what would appear to be the basics was surprising. The vast majority of respondents used only daytime blood pressure in clinical decision making however the threshold for commencing treatment was higher than the definition of hypertension. Obviously thresholds will vary dependent on an individual's concomitant cardiovascular risk factors but even in the clinical scenarios, there was very little agreement on treatment or whether or not ABPM was useful.

## Study 4 – Expert versus computer based algorithm in ABPM diagnosis

### ***Background***

The results from studies 1-3 showed that clinicians, faced with identical ABPM data, did not agree on a decision whether to recommend antihypertensive medication or not. One possible conclusion is that if experts cannot agree, the only alternative would be to use computerised assessment so as to standardise ABPM interpretation.

The only ABPM software program providing an interpretative analysis according to the measurement guideline of the European Society of Hypertension (ESH) is the dabl<sup>®</sup> ABPM system (dabl Limited, Ireland. [www.dabl.ie](http://www.dabl.ie)), and the objective of the study was to

assess the accuracy of diagnostic reporting between clinicians and this computerised methodology. In study 1, the data presented to the observers allowed for comparison of treatment decisions but as the dabl<sup>®</sup> ABPM system does not (as yet) make treatment suggestions the comparison between the dabl<sup>®</sup> ABPM system and the observers was limited to interpretative (diagnostic) decisions.

## **Methods**

*Observer selection:* dabl Educational Trust is an independent organization whose website documents all available validated ambulatory and self blood pressure monitors. The advisory board of the trust consists of 26 members, all international experts in hypertension. All were invited to act as observers.

*Observer questionnaire:* Each member was sent a questionnaire to ascertain the criteria applied for ABPM and the thresholds of abnormality used by each observer. (Table 6.5)

*ABPM reports:* 12 ABPMs, representative of common ABPM patterns, were selected: normal ABPM record with dipping pattern; white coat hypertension in first hour – normal day and night-time BP (Figure 6.2); white coat effect first hour – moderate day and night-time hypertension; hypertension (moderate to severe); non-dipping pattern (normal day, similar BP at night ); non-dipping pattern (normal day, more elevated at night ); non-dipping pattern (moderate Hypertension); isolated systolic hypertension; isolated diastolic hypertension; autonomic failure: daytime hypotension with nocturnal hypertension. Each observer was asked to complete a questionnaire and to evaluate the ABPMs which were anonymised and presented as Spacelabs reports (Figure 6.2).



10	The ABPM suggests moderate daytime systolic and diastolic hypertension (168 mmHg / 102 mmHg) and severe night-time systolic and diastolic hypertension (157 mmHg / 101 mmHg).	Dipping Status 4.3% / -1.0%				
		BP Diagnosis	Dipper	Non Dipper	Not Stated	Total
		HBP		8	9	17

11	The ABPM suggests moderate 24-hour isolated systolic hypertension (170 mmHg / 82 mmHg daytime, 147 mmHg / 65 mmHg night-time).	Dipping Status 11.9% / 16.3%				
		BP Diagnosis	Dipper	Non Dipper	Not Stated	Total
		ISH	3	2	9	14
		HBP		1	2	3
		Total	3	3	11	17

12	The ABPM suggests moderate 24-hour systolic and diastolic hypertension (161 mmHg / 104 mmHg daytime, 147 mmHg / 91 mmHg night-time) with a white-coat effect (187 mmHg / 134 mmHg).	Dipping Status 8.7% / 14.2%				
		BP Diagnosis	Dipper	Non Dipper	Not Stated	Total
		HBP	3	6	8	17

Summary

Common patterns were not diagnosed by the experts in a number of instances: isolated diastolic hypertension (three experts in ABPM 3); isolated systolic hypertension (three experts in ABPM 11). On occasions incorrect diagnoses were made, for example in ABPM 2 (Figure 6.3), five experts diagnosed isolated systolic hypertension although the blood pressure levels were normal; in ABPM 5, seven experts identified abnormalities in spite of normal day and night-time blood pressures.

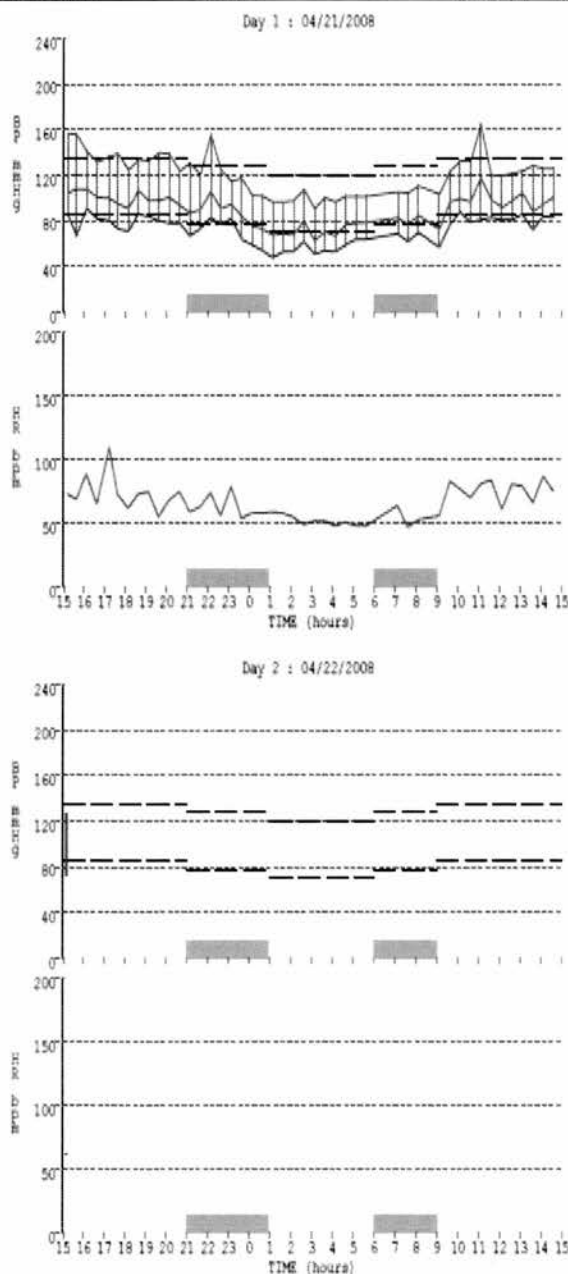
Six of the ABPMs had a nocturnal dip in systolic BP of less than 10%. In the three ABPMs (1, 6 and 8) who had optimal daytime pressure and a higher night-time pressure, this was identified clearly in 50/51 reports. However, once the drop became positive, there were conflicting diagnoses. In ABPM 4, which had optimal daytime mean pressure but an upper normal night-time mean pressure with just five pressures above normal over the whole ABPM, eight experts indicated a normal non-dipper pattern as suggested by the mean pressures; two indicated a normal dipper pattern, one nocturnal hypertension and one diagnosed autonomic failure. Where hypertensive patients were

*dabl<sup>®</sup> ABPM system:* Blind to the observers, the corresponding dabl<sup>®</sup> reports were generated (Figure 6.3) and the automatic interpretations, generated according to the ESH guideline [O'Brien *et al* 2005], were extracted.

*Comparison of observer v dabl<sup>®</sup> ABPM data:* Both sets of data were analysed for inter-observer variability, observer v dabl<sup>®</sup> ABPM consistency and the time taken for observer reportage was noted. The analysis consisted of identifying whether or not hypertension was present and, if so, the type of hypertension e.g. white coat hypertension. Comment on dipping status was also analysed, assuming this was stated or could be inferred e.g. lower nocturnal pressure than daytime pressure.

**Figure 6.2:** Example pages from Spacelabs report

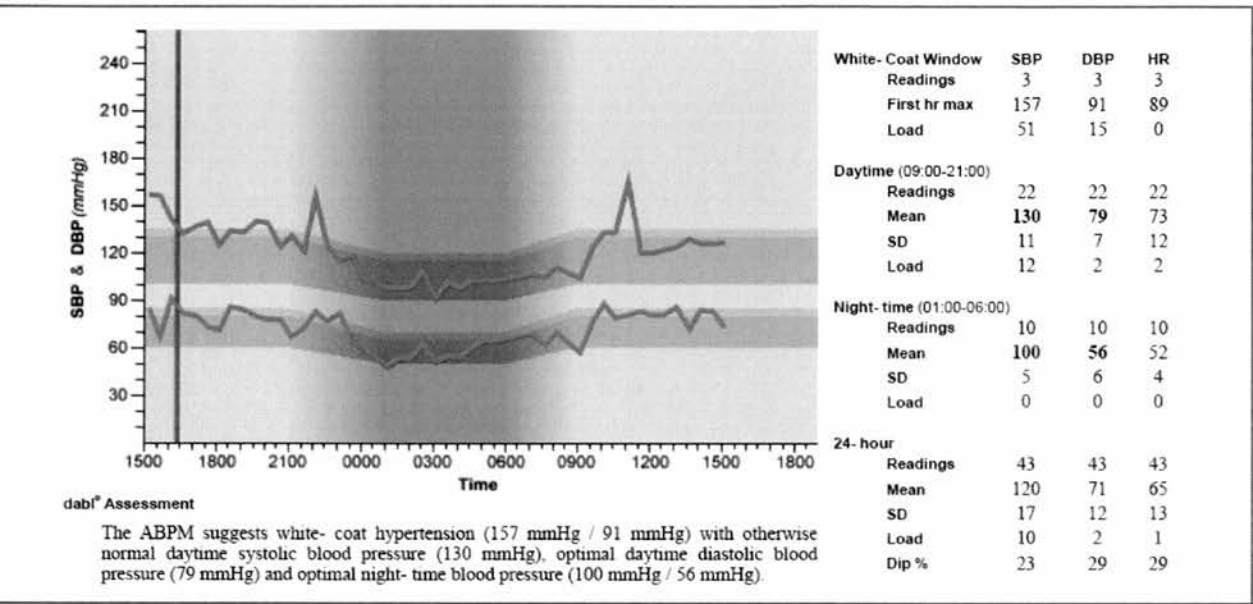
ABP Raw Data Graph Patient 2 04/21/2008 Page 2 of 7



ABP Summaries Patient 2 04/21/2008 Page 7 of 7

SUMMARY				
	MIN	MEAN	MAX	STD
Systolic	91 (1-03:08)	122	165 (1-11:08)	18.12 mmHg
Diastolic	48 (1-01:08)	72	91 (1-16:08)	11.87 mmHg
MAP	63	90	118	13.41 mmHg
Heart Rate	47	66	110	13.55 BPM
Percent of Systolic Readings above period limits: 21.7 %				
Percent of Diastolic Readings above period limits: 13.0 %				
Percent of time Systolic was above period limits: 19.4 %				
Percent of time Diastolic was above period limits: 12.5 %				
SUMMARY PERIOD: 9:00 to 21:00				
	MIN	MEAN	MAX	STD
Systolic	104 (1-09:10)	132	165 (1-11:08)	13.04 mmHg
Diastolic	57 (1-09:10)	79	91 (1-16:08)	7.31 mmHg
MAP	73	98	118	8.37 mmHg
Heart Rate	55	74	110	11.85 BPM
Percent of Systolic Readings > 135 mmHg: 32.0 %				
Percent of Diastolic Readings > 85 mmHg: 16.0 %				
Percent of time Systolic > 135 mmHg: 26.9 %				
Percent of time Diastolic > 85 mmHg: 14.6 %				
SUMMARY PERIOD: 21:00 to 1:00				
	MIN	MEAN	MAX	STD
Systolic	102 (1-00:38)	121	156 (1-22:08)	17.20 mmHg
Diastolic	54 (1-00:38)	68	83 (1-22:08)	10.64 mmHg
MAP	73	86	106	10.50 mmHg
Heart Rate	54	62	79	9.04 BPM
Percent of Systolic Readings > 128 mmHg: 25.0 %				
Percent of Diastolic Readings > 78 mmHg: 25.0 %				
Percent of time Systolic > 128 mmHg: 21.4 %				
Percent of time Diastolic > 78 mmHg: 28.6 %				
SUMMARY PERIOD: 1:00 to 6:00				
	MIN	MEAN	MAX	STD
Systolic	91 (1-03:08)	100	108 (1-02:38)	4.55 mmHg
Diastolic	48 (1-01:08)	56	64 (1-05:08)	5.70 mmHg
MAP	63	73	80	5.98 mmHg
Heart Rate	48	53	59	4.11 BPM
Percent of Systolic Readings > 120 mmHg: 0.0 %				
Percent of Diastolic Readings > 70 mmHg: 0.0 %				
Percent of time Systolic > 120 mmHg: 0.0 %				
Percent of time Diastolic > 70 mmHg: 0.0 %				
SUMMARY PERIOD: 6:00 to 9:00				
	MIN	MEAN	MAX	STD
Systolic	105 (1-07:38)	107	111 (1-08:08)	3.21 mmHg
Diastolic	62 (1-07:38)	68	70 (1-08:08)	4.36 mmHg
MAP	77	82	85	4.16 mmHg
Heart Rate	47	57	64	8.62 BPM
Percent of Systolic Readings > 128 mmHg: 0.0 %				
Percent of Diastolic Readings > 78 mmHg: 0.0 %				
Percent of time Systolic > 128 mmHg: 0.0 %				
Percent of time Diastolic > 78 mmHg: 0.0 %				

**Figure 6.3:** Extract from the corresponding 1-page dabl report



Results

*Observers:* Seventeen of 26 invited experts completed the questionnaire (Appendix 6.2) and the remaining 9 did not respond to the invitation.

*ABPM reports:* The results of the questionnaire on the use of ABPM are shown in Table 6.5. There was some variation in the thresholds. Those that matched ESH or IDACO guidelines are indicated in the table.

Each of the questionnaires for the 12 ABPM patterns were coded and analysed. The comparative analyses between the automatically interpreted dabl® ABPM reports and the observer interpreted SpaceLabs reports are summarised in Table 6.6.

Table 6.5 Summary results of questionnaire analysis

Questionnaire responses		17	
How often do you use ABPM to confirm a diagnosis of hypertension?	Always	3	
	In most cases	8	
	Sometimes	6	
Do you use ABPM to confirm a diagnosis in low risk patients?	Yes	14 <sup>a</sup>	
	No	3	
Do you use ABPM to confirm diagnosis in patients with target organ damage?	Yes	11 <sup>a</sup>	
	No	6	
Do you use ABPM to confirm diagnosis in other circumstances?	To ascertain treatment efficacy	7	
	In suspected masked hypertension	5	
	In suspected white coat hypertension	4	
	To check home blood pressure	4	
	To determine BP variability	3	
	To diagnose resistant hypertension	2	
	In elderly patients with hypertension	2	
	In newly diagnosed hypertensive patients	2	
	In patients with previous CV event	2	
	In patients without target organ damage	1	
	In patients with suspected hypotension	1	
	For annual check-up	1	
	In symptomatic patients	1	
	In pregnant women with hypertension	1	
	In patients under 40 years of age with hypertension	1	
Do you have a threshold level for normality?	Daytime SBP/DBP	140 / 85	1
		135 / 85 (ESH) <sup>b</sup>	10
		130 / 85 (IDACO) <sup>b</sup>	3
		130 / 80	2
		None	1
	Night -time SBP/DBP	125 / 75	1
		120 / 75	1
		120 / 70 (ESH) <sup>b</sup>	10
		115 / 75	1
		115 / 65	1
		110 / 70 (IDACO) <sup>b</sup>	1
		None	2
	24-hour SBP/DBP	130 / 80 (ESH) <sup>b</sup>	10
		125 / 80 or 125 / 79 (ESH) <sup>b</sup>	3
		125 / 75 (IDACO) <sup>b</sup>	1
		120 / 75	1
		None	2
	How long did the 12 ABPM interpretations take you in minutes? <sup>c</sup>	Median	32 min 30 sec
		Mean	41 min 11 sec
SD		29 min 37 sec	
Maximum		120 min	
Minimum		10 min	
Notes			
a Includes one "Yes" by inference to "Always" response in the leading question.			
b ESH thresholds Day time 130-135 / 85 Night -time 120 / 70 24-hour 125-130 / 80 IDACO thresholds Day time 130 / 85 Night -time 110 / 70 24-hour 125 / 75			
c There was 16 responses. One responder gave 3 minutes and one 1-2 minutes. Counting these as "per ABPM", they were multiplied by 12 to give 36 and (using 1.5 for 1-2) 18 minutes respectively.			

**Table 6.6 Summary of dabl vs. expert interpretation**

**dabl® Generated Report**

ABPM

BP levels as recommended by ESH guidelines

**Analysis of Diagnosis and Dipping Status**

Results as indicated by guidelines are highlighted

1

The ABPM suggests optimal daytime blood pressure (122 mmHg / 69 mmHg) and mild night-time systolic and diastolic hypertension (132 mmHg / 79 mmHg).

	Dipping Status-9.0% / -12.9%			
BP Diagnosis	Dipper	Non Dipper	Not Stated	Total
Night HBP		16		16
Normal			1	1
Total		16	1	17

2

The ABPM suggests white-coat hypertension (157 mmHg / 91 mmHg) with otherwise normal daytime systolic blood pressure (130 mmHg), optimal daytime diastolic blood pressure (79 mmHg) and optimal night-time blood pressure (100 mmHg / 56 mmHg).

	Dipping Status24.2% / 29.1%			
BP Diagnosis	Dipper	Non Dipper	Not Stated	Total
Normal	4		8	12
ISH	4		1	5
Total	8		9	17

3

The ABPM suggests mild 24-hour isolated diastolic hypertension (128 mmHg / 96 mmHg daytime, 110 mmHg / 77 mmHg night-time).

	Dipping Status14.0% / 17.7%			
BP Diagnosis	Dipper	Non Dipper	Not Stated	Total
24h IDH	3		10	13
Day IDH, Night HBP		1		1
Normal	2		1	3
Total	5	1	11	17

4

The ABPM suggests optimal daytime blood pressure (123 mmHg / 72 mmHg), normal night-time systolic blood pressure (116 mmHg) and optimal night-time diastolic blood pressure (62 mmHg).

	Dipping Status4.2% / 11.3%			
BP Diagnosis	Dipper	Non Dipper	Not Stated	Total
Normal	2	8	5	15
Night HBP		1		1
Autonomic Failure		1		1
Total	2	10	5	17

5

The ABPM suggests white-coat hypertension (157 mmHg / 92 mmHg) with otherwise normal 24-hour blood pressure (130 mmHg / 84 mmHg daytime, 117 mmHg / 68 mmHg night-time).

	Dipping Status11.5% / 20.2%			
BP Diagnosis	Dipper	Non Dipper	Not Stated	Total
Normal	3		7	10
Night HBP		3		3
Day HBP	1			1
IDH		1	2	3
Total	4	4	9	17

6

The ABPM suggests optimal daytime blood pressure (116 mmHg / 72 mmHg) and mild night-time systolic and diastolic hypertension (134 mmHg / 77 mmHg).

	Dipping Status-13.7% / -4.1%			
BP Diagnosis	Dipper	Non Dipper	Not Stated	Total
Night HBP		16		16
Day Low, Night HBP		1		1
Total		17		17

7

The ABPM suggests severe daytime systolic and diastolic hypertension (172 mmHg / 116 mmHg) and moderate night-time systolic and diastolic hypertension (144 mmHg / 90 mmHg).

	Dipping Status16.3% / 21.7%			
BP Diagnosis	Dipper	Non Dipper	Not Stated	Total
HBP	7		10	17

8

The ABPM suggests optimal daytime blood pressure (112 mmHg / 66 mmHg) and mild night-time systolic and diastolic hypertension (131 mmHg / 79 mmHg) with a white-coat effect (143 mmHg / 79 mmHg).

	Dipping Status-13.9% / -16.2%			
BP Diagnosis	Dipper	Non Dipper	Not Stated	Total
Night HBP		16		16
Night ISH		1		1
Total		17		17

9

The ABPM suggests moderate 24-hour systolic and diastolic hypertension (166 mmHg / 102 mmHg daytime, 143 mmHg / 87 mmHg night-time) with a white-coat effect (183 mmHg / 115 mmHg).

	Dipping Status15.0% / 17.3%			
BP Diagnosis	Dipper	Non Dipper	Not Stated	Total
HBP	4	4	9	17

also non-dippers, the tendency was not to indicate it (nine experts in the case of ABPM 10 and eight in the case of ABPM 12) or, where the dip was close to 10%, to indicate a dip (three experts in the case of ABPM 12).

In the largest dippers [24% (ABPM 2, Figure 6.3) and 16% (ABPM 7)] no experts indicated a non-dipping pattern but only eight and seven experts respectively indicated the dipping pattern. Despite dips of 15% and 11.5% respectively for ABPMs 9 and 5, dipping and non-dipping patterns were each indicated by four experts in both instances.

An indication of the severity of hypertension was not made in a number of ABPMs: (seven experts in ABPM 7; 11 experts in ABPM 9; 14 experts in ABPM 11; nine experts in ABPM 12).

White coat hypertension and white coat effect, although obvious in many instances, were not identified in five patients (by 12 physicians in Patient 2; by nine physicians in Patient 5; by 14 physicians in Patient 8; by 14 physicians in Patient 9; by 15 physicians in Patient 12).

## ***Conclusion***

The advantages of ABPM have been discussed and examined at some length throughout this thesis however it could be argued that these advantages are in part due to one distinct benefit in blood pressure measurement – it removes human interpretation and gives an unbiased view of blood pressure i.e. there is no white coat effect, observer error or terminal digit preference. However, relying on human interpretation of the measurements re-introduces some of that error. The level of complexity needed for the results in study 4 demonstrate that making a diagnosis is hugely variable, even before

any treatment decisions are made. This series of four studies very clearly demonstrates the lack of consensus in all areas from the definition of hypertension to who should be assessed with ABPM and which patients should be treated. One of the most surprising results is the apparent need for hypertension to be confirmed by ABPM in those patients with already documented hypertensive target organ damage (described by 11 of 39 physicians in study 3 and 11 of 17 in study 4).

There is currently a great deal of controversy surrounding the use of ABPM and whether or not this could be replaced by self monitoring in the management of hypertension (Parati *et al* 2009, Verdecchia *et al* 2009). Proponents of ABPM correctly point out the wealth of evidence from longitudinal studies denoting its' prognostic superiority. Also, only ABPM can reveal nocturnal BP/dipping status which can be used for further stratification of an individuals' cardiovascular risk. However, the ability to obtain this information is only of use if it is paid any heed. The results outlined in this chapter specifically demonstrate that whilst hypertension specialists may recognise the importance of nocturnal BP dipping &/or nocturnal blood pressure, the vast majority still only use awake-time blood pressure when it comes to deciding on whether or not antihypertensive therapy should be initiated.

The level of variance in reporting ABPM could be removed by utilising intelligent computer-generated interpretative reports to standardise ABPM interpretation. The only ABPM software program providing an interpretative analysis of recorded data is the dabl® ABPM Program (dabl Limited, 34 Main Street, Blackrock, Co. Dublin, Ireland. Tel: +353 (01) 278 0247. [www.dabl.ie](http://www.dabl.ie)). Computer-generated reports should be seen, however, as a means of standardising the analysis of data. The decision regarding



treatment should still rest with the physician. I do not think that decisions regarding treatment should be included in any computer based algorithm. Whilst there is an argument for 'the lower the better' when treating blood pressure, as in the treatment of cholesterol, each case does need to be treated individually, wherein lies the art of medicine. For example, a 46 year old male smoker with type 2 diabetes, microalbuminuria and an awake-time BP on ABPM of 160/100mmHg (defined as hypertensive by a computer generated algorithm-e.g. patient 12 in study 4) would receive antihypertensive therapy from (I hope) any physician. However, a 72 year old patient on warfarin for recurrent transient ischaemic attacks with an awake-time BP of 140/85mmHg may not necessarily require antihypertensive treatment – the risk of drug induced postural hypotension and therefore falls risk in a patient on warfarin needs to be weighed up against the potential benefit of lowering BP in a patient with known vascular disease. Such complex decisions can only be made by physicians.

If the problems of ABPM reporting are not addressed by computer generated reporting, and bearing in mind most physicians treat awake-time pressure only, does it follow that self blood pressure monitoring (SBPM) may slowly replace ABPM ? (Parati *et al* 2009)

Perhaps ABPM could take place as the first investigation, thereby delineating nocturnal dipping status for risk stratification. The information in chapter 3 illustrates that the nocturnal dip doesn't change when expressed as a continuous variable therefore perhaps it need only be checked once. Further investigation of out of office BP e.g. BP measurement in titration of antihypertensive medications could then be done using self blood pressure monitoring.

However, first we need to be sure that SBPM gives the same information as awake-time ABPM. This is addressed in chapter 7

# Appendix 6.1- Clinical Decision-making using Ambulatory Blood Pressure Monitoring (ABPM) and Self (Home) Blood Pressure Monitoring (SBPM)

Please describes yourself in each of the following four categories (please paste this symbol ✓)

Hospital-base		Physician		Senior position		Special-interest in hypertension	
Primary Care-based		Nurse		Trainee		No special interest	

The number of hypertensive patients I care for in a typical year is	
---	--

The number of ABPM reports I consider in a typical year is	
--	--

I currently use ABPM *before considering treatment* in patients .....

Who exhibit variability in office BP	almost always		often		occasionally		hardly ever	
Who are elderly	almost always		often		occasionally		hardly ever	
Who are young and low risk	almost always		often		occasionally		hardly ever	
Who have target organ damage	almost always		often		occasionally		hardly ever	

Which of the following aspects of the ABPM report influence your response?

Awake/daytime average BP	almost always		often		occasionally		hardly ever	
--------------------------	---------------	--	-------	--	--------------	--	-------------	--

Sleep/nighttime average BP	<b>almost always</b>		<b>often</b>		<b>occasionally</b>		<b>hardly ever</b>	
24 hour average BP	<b>almost always</b>		<b>often</b>		<b>occasionally</b>		<b>hardly ever</b>	

What would be your threshold ABPM measurement for advising treatment in a healthy 45-year old male at relatively low CV risk? *Please fill in those that are relevant to you.*

Awake/daytime average BP – threshold for treatment would be ...	<b>SBP</b>		<b>DBP</b>		<b>mmHg</b>
Sleep/nighttime average BP – threshold for treatment would be ...	<b>SBP</b>		<b>DBP</b>		<b>mmHg</b>
24 hour average BP – threshold for treatment would be ...	<b>SBP</b>		<b>DBP</b>		<b>mmHg</b>

I currently use ABPM for monitoring the response to antihypertensive therapy in patients  
.....

Who exhibit variability in office BP	<b>almost always</b>		<b>often</b>		<b>occasionally</b>		<b>hardly ever</b>	
Who appear to be 'drug-resistant'	<b>almost always</b>		<b>often</b>		<b>occasionally</b>		<b>hardly ever</b>	
Who appear to have a 'white-coat' response	<b>almost always</b>		<b>often</b>		<b>occasionally</b>		<b>hardly ever</b>	
To confirm that target BP has been achieved	<b>almost always</b>		<b>often</b>		<b>occasionally</b>		<b>hardly ever</b>	

For uncomplicated patients already on antihypertensive therapy what ABPM measurements indicate successful therapy i.e. no further escalation required? *Please fill in those that are relevant to you.*

Awake/daytime average BP target would be ...	<b>SBP</b>		<b>DBP</b>		<b>mmHg</b>
Sleep/nighttime average BP target would be ...	<b>SBP</b>		<b>DBP</b>		<b>mmHg</b>
24 hour average BP target would be ...	<b>SBP</b>		<b>DBP</b>		<b>mmHg</b>

I currently use SBPM for managing patients .....

Who are being considered for drug therapy	<b>almost always</b>		<b>often</b>		<b>Occasionally</b>		<b>hardly ever</b>	
Who are already on treatment	<b>almost always</b>		<b>often</b>		<b>Occasionally</b>		<b>hardly ever</b>	

What would be your threshold SBPM measurement for advising treatment in a healthy 45-year old male at relatively low CV risk?

SBPM average BP – threshold for treatment would be ...	<b>SBP</b>		<b>DBP</b>		<b>mmHg</b>
--	------------	--	------------	--	-------------

## Clinical Scenarios – does ABPM help?

We would like you indicate whether or not you would advise initiating antihypertensive in each of the following clinical scenarios. We understand that this may oversimplify the factors that are involved in the real world but we would like you to provide a yes (Y) or no (N) based on what is provided. You should make the following assumptions: (i) The office/clinic BP is the average of at least 2 visits, (ii) Family history (FH) refers to a first degree relative who has had a myocardial infarction (MI) or stroke (CVA) before the age of 60, (iii) All patients have a normal plasma urea and creatinine, and (iv) Cardiovascular Disease or Target Organ Damage (CVD/TOD) includes a range of conditions such as definite ECG evidence of left ventricular hypertrophy (LVH), peripheral vascular disease (PVD), MI or CVA.

#	Sex	Age	Office BP	FH	CVD/TOD	DM	Smoker	Chol/HDL ratio	Awake ABP	Sleep ABP	Treat (Y/N)
1	M	64	148/90	N	MI	N	N	5.8	125/70	114/67	
2	M	36	168/108	Y	N	N	Y	3.3	130/70	110/60	
3	F	45	162/100	N	N	N	N	3.8	134/83	118/64	
4	F	31	164/102	N	N	N	N	3.5	142/92	136/84	
5	M	40	146/87	N	N	N	N	4.1	136/88	124/68	
6	F	64	138/86	N	N	Y	N	4.4	142/84	139/82	
7	F	78	194/90	N	PVD	N	N	5.0	142/90	116/70	
8	F	30	168/104	N	N	N	N	3.6	122/68	111/60	
9	F	28	148/100	N	N	N	N	3.0	128/75	108/64	
10	M	58	152/100	N	N	N	N	4.3	132/87	145/80	
11	M	38	170/110	Y	N	N	Y	3.1	145/88	122/75	
12	M	46	156/94	N	N	N	N	4.4	134/78	140/80	
13	F	33	162/100	Y	N	N	Y	5.0	138/84	120/78	
14	M	41	145/86	N	N	N	N	4.3	135/87	142/91	
15	M	38	140/90	N	N	N	Y	5.6	140/90	118/78	
16	F	76	162/106	N	CVA	N	N	6.0	128/65	108/59	
17	M	56	162/108	N	N	N	N	4.4	146/95	130/82	
18	F	66	148/88	N	N	Y	N	4.7	122/72	114/64	
19	M	56	156/102	N	N	N	N	4.0	132/78	116/70	
20	M	37	139/88	N	N	N	N	4.6	145/89	128/78	
21	F	80	188/87	N	PVD	N	N	5.4	134/82	119/77	

## Appendix 6.2: Expert participants from the dabl® Educational Trust Advisory Board

Dr. Roland Asmar, Société Française D'Hypertension Artérielle, Filiale de la Société Française de Cardiologie, 15, rue de Cels-75014, Paris, FRANCE.

Professor Denis L. Clement, Afdeling Hart-en Vaatziekten, Universitair Ziekenhuis, De Pintelaan 185, B-9000 Gent, BELGIUM

Dr. Peter De Leeuw, interne geneeskunde, academisch ziekenhuis, P. Debyelaan 25, postbus 5800, 6202 AZ Maastricht, The Netherlands.

Professor Robert Fagard, Katholieke Universiteit Leuven, Hypertensie en Cardiovasculaire Invalidatie Eenheid, Inwendige Geneeskunde-Cardiologie, U.Z. Gasthuisberg, Herestraat 49, 3000 Leuven, BELGIUM.

Dr. John Graves, Division of Hypertension and the Division of Nephrology, Mayo Medical School, The Mayo Clinic, Rochester, Minnesota, US

Professor Yutaka Imai, Department of Clinical Pharmacology and Therapeutics, Tohoku University Graduate School. of Pharmaceutical Science and Medicine, Tohoku University Hospital Clinical Trial Center, 1-1 Seiryochō Aobaku, Sendai 980-8574, JAPAN

Professor Giuseppe Mancia, Università Degli Studi di Milano-Bicocca, Cattedra di Medicina Interna Ospedale San Gerardo Dei Tintori, Via Donizetti, 106, 20052 Monza, ITALY.

Dr. Martin G. Myers, Division of Cardiology, Sunnybrook Health Sciences Centre, A202 - 2075 Bayview Avenue, Toronto, Ontario M4N 3M5, CANADA

Professor Eoin O'Brien, Conway Institute of Biomolecular and Biomedical Research, University College Dublin, Belfield, Dublin 4. IRELAND

Professor. Paul Padfield, Department of Medicine, Western General Hospital, Edinburgh EH4 2XU, SCOTLAND

Dr. Paolo Palatini, Dipartimento di Medicina Clinica e Sperimentale, Università di Padova, Via Giustiniani 2, I-35128 Padua, ITALY

Professor Gianfranco Parati, Dept Clinical Medicine, Prevention and Applied Biotechnologies, University of Milano-Bicocca and Ospedale San Luca, IRCCS, Istituto Auxologico Italiano, 20149 Milan, Via Spagnoleto 3, ITALY.

Professor Jan Staessen, Katholieke Universiteit Leuven, Hypertensie en Cardiovasculaire Revalidatie Eenheid, Inwendige Geneeskunde-Cardiologie, U.Z. Gasthuisberg, Herestraat 49, 3000 Leuven, BELGIUM.

Dr. George Stergiou, Hypertension Center, Third University Dept of Medicine, Sotiria Hospital, Athens, GREECE

Dr. Paolo Verdecchia, Dipartimento Malattie Cardiovascolari, Università di Perugia, Ospedale R. Silvestrini, Andrea delle Fratte 06156 Perugia, ITALY

Professor Bernard Waeber, Centre Hospitalier Universitaire Vaudois, Division D'Hypertension, Département de médecine interne, 1011 Lausanne, SWITZERLAND.

Professor William White, Section of Hypertension and Vascular Diseases, The University of Connecticut Health Center, 263 Farmington Avenue, Farmington, Connecticut 06030-3940, U.S.

## Chapter 7

### **Self blood pressure monitoring: a worthy substitute for ambulatory blood pressure.**

#### *Background*

Although the evidence that 'out of office' blood pressure better predicts cardiovascular outcome than clinic readings is strong [Perloff et al 1983, Clement et al 2003, Ohkubo et al 2004a, Kikuya et al 2005, Dolan et al 2005, Pickering et al 2006] there remains a great deal of uncertainty as to how this technology should be used in clinical practice. ABPM has come to be regarded as the 'gold standard', probably because it has been studied more extensively than SBPM [Pickering 1995, O'Brien et al 2003]. Whilst ABPM has been shown to be cost effective in establishing the diagnosis of true hypertension [Lorgelly et al 2003, Krakoff 2006] the equipment remains expensive and may not be practicable for the diagnosis and long-term management of hypertension in a primary care setting [Parati et al 2009]. Electronic self-monitors are at least an order of magnitude cheaper than ambulatory devices and are increasingly being used by the public with or without clinician support. Up to 50% of the hypertensive population in the USA admits to using such a monitor [Gallup 2006] and, even in the UK this figure is as high as 10% of the general population [McManus et al 2007].

National and international guidelines [Pickering 1996, JNC VI 1997, Williams et al 2004, O'Brien et al 2005] have all indicated the potential value of SBPM but, until recently, detailed advice on how such methodology should be applied have been lacking. In 2008 the ESH published detailed guidelines on how patients and health care professionals should use SBPM to diagnose hypertension [Parati et al 2008] and, whilst



these were somewhat empirical, they have been endorsed by AHA, ASH [Pickering et al 2008] and a recent British national conference [McManus et al 2008]. The guidance advises that BP be measured (in duplicate), morning and evening for 7 days (28 readings) and that the first day's results (generally higher in most studies) are discarded. The final BP is therefore an average of 24 measurements.

### ***Hypothesis***

The average blood pressure derived from the ESH home BP monitoring schedule is not significantly different to the daytime average blood pressure obtained from ABPM.

### ***Methods***

#### *Study population*

The Edinburgh Direct Access ABPM service has been running for over 10 years [Richards et al 2004] and allows primary care physicians to obtain ABPM, generally to confirm or exclude hypertension. Routinely referred patients were invited, treated or untreated, to participate in this comparative study. Patients with major illness, inability to use the home monitor, atrial fibrillation or pregnancy were excluded. In groups of six, patients were allocated to perform either SBPM or ABPM first i.e. all patients had a single episode of monitoring with each device. All were taught, by research nurses, how to use a validated self-monitor ("WatchBP Home", Microlife [Stergiou et al 2007]) and written instructions were provided. Patients were 'block' randomized as above but not fully randomized as I was not present on-site during the day to day running of the study in order to coordinate this.

### *Blood pressure measurement*

SBPM was performed 4 times per day, as per the ESH guidelines. Patients made two measurements in the morning between 7am and 9am and 2 in the evening between 7pm and 9pm. The self-monitoring device used in the study is programmed for a sixty second delay between activating the first BP measurement and cuff inflation and sixty seconds between readings. After each duplicate reading, an average is displayed and patients asked to note this down. All patients were aware of the memory function on the device and the written readings were compared to establish reporting accuracy. After seven days, an average of 24 readings is displayed (first day readings automatically disregarded for habituation) and this figure was used for comparison with the awake-time average from the ABPM.

ABPM was performed using a non-invasive oscillometric device (Spacelabs 90207 – Spacelabs Inc., Redmond, Washington, USA) under standardised conditions – 24 hr recordings were made as that is the standard operating procedure for the service. An appropriate sized cuff was applied to the non-dominant arm and readings obtained at 30' intervals. Awake-time averages were calculated on the basis of patient diaries [Stewart et al 1993] and this was compared to mean self-measured blood pressure. The raw BP data are downloaded to a Microsoft Access database then transferred to a Microsoft excel spreadsheet for analysis. All patients included had  $\geq 20$  BP measurements with both ABPM and SBPM.

Both ABPM and SBPM used the same arm and cuff size for measurements.

Both BP monitoring procedures (24-hours of ABPM and 1 week of SBPM) took place within an eight-day period. All patients gave written informed consent after at least 24 hours of receiving a written information sheet and the local ethics committee approved the study.

A total of 87 subjects were enrolled, in accordance with the number accepted by the AAMI [AAMI 1987] and the original British Hypertension Society protocol for the validation of BP monitoring devices [O'Brien et al 1990]. Age, smoking status, ethnicity and presence or absence of diabetes was noted and all patients were asked to complete a short questionnaire on the experience of each blood pressure monitoring period.

Hypertension was defined, a priori, as  $\geq 135/85$  mmHg on SBPM or awake average on ABPM [JNC VI 1997, O'Brien et al 2005].

### **Statistics**

The hypothesis to be tested was that there is no difference between ABPM and SBPM in terms classification of 'hypertensive' or 'normotensive' or blood pressure measured as a continuous variable i.e. to prove the validity of the ESH monitoring schedule.

Classification as hypertensive or normotensive and how many subjects change category is expressed as a percentage. To remove the possibility of subjects being classified the same as a result of chance, Cohen's Kappa statistic ( $\kappa$ ) is also used. This is a relative statistic with a value of 0 denoting no agreement and 1 denoting perfect agreement. Comparison of blood pressure as a continuous variable is examined using

the intra-class correlation coefficient (ICC – also a relative statistic) and using a repeatability coefficient / Bland Altman plot [Bland et al 1986, 1996].

All blood pressure results are expressed as mean  $\pm$  SD.

## **Results**

All subjects completed the study. The mean age of participants was 57 ( $\pm$  12) and 48% were male. Approximately a quarter (27%, n=23) were on antihypertensive treatment, 8% (n=7) were smokers and 7% (n=6) had diabetes.

The awake time average ABPM was 141/86 ( $\pm$ 11/10) mmHg and there was no significant impact on this figure if the first 2 hours of BP readings of the ABPM, the so-called 'white coat window' [Owens et al 1999], were removed (data not shown).

Average SBPM, 142/87 ( $\pm$ 12/10) mmHg was no different from the awake ABPM and there was no evidence of an order effect i.e. the second period of monitoring was not significantly different from the first (data not given).

With respect to classification of hypertensive or not, SBPM was concordant with ABPM in 87% of cases,  $\kappa$ =0.56 (95% CI 0.34-0.78). ICC and repeatability coefficients describe agreement when BP is expressed as a continuous variable between methods (table 7.1). Figure 7.1 illustrates the Bland Altman plot for SBPM vs. ABPM.

## *Patient preference*

Subject questionnaires were completed by 83 of 87 subjects. Of these, 81% preferred SBPM to ABPM. The main reasons for preference given were: the ability to instantly

see their BP; being more “in control”; less embarrassment in public and no interference in sleep. Thirteen subjects reported difficulty in adhering to the time constraints of the SBPM but only 2 reported difficulty in completing one week of monitoring. Three subjects reported an increase in anxiety during SBPM.

The 19% of subjects who preferred ABPM indicated that this was because it was “over in 24 hours”.

Table 7.1 Level of agreement between ABPM and SBPM for blood pressure when expressed as a continuous variable

	<b>SBPM vs. ABPM</b>	
	<b>Systolic BP</b>	<b>Diastolic BP</b>
<b><u>Intra class correlation (95% CI)</u></b>	<b>0.72 (0.57-0.82)</b>	<b>0.89 (0.83-0.93)</b>
<b><u>Repeatability coefficient (95% CI)</u></b>	<b><u>5.2 (4.1-6.2)</u></b>	<b><u>5 (4.1-5.8)</u></b>

*Reporting Accuracy*

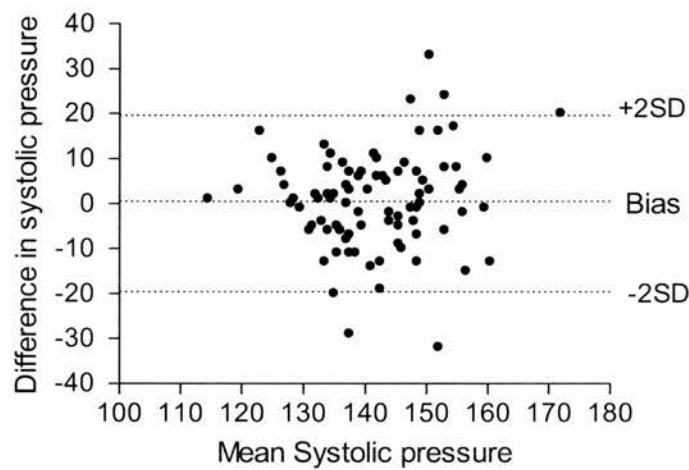
The memory was checked and compared to the self-reported blood pressure results following SBPM with 100% accuracy documented.

*Time required*

All SBPM and ABPM monitors were fitted by the same three nursing staff throughout the study. The standard appointment time for fitting an ambulatory device is 30 minutes and this does not include time to download the monitor after recording. Although the

exact timing was not part of the study, the time taken to explain and demonstrate self monitoring was substantially less, between 10 & 15 minutes per subject.

Figure 7.1 Bland Altman plot of systolic pressure comparing SBPM with ABPM



**Discussion**

Ambulatory blood pressure monitoring is firmly established as the reference standard for non invasive blood pressure monitoring [Pickering 1996, O'Brien et al 2003], backed up by a significant amount of literature. Currently, there is debate over the exact place of ambulatory and self monitoring [Parati et al 2009, Verdecchia et al 2009]. However, there is consensus that self monitoring does provide a cheap, patient-friendly method of blood pressure monitoring in the management of hypertension. The ESH described a schedule of self-monitoring which was somewhat pragmatic but until now has lacked any real evidence. This study has demonstrated for the first time that mean BP obtained by SBPM using the ESH/ASH guidelines is no different to awake-time BP on ABPM.

The agreement between hypertensive and normotensive classification was moderate but this was only to be expected given the well known problems with reproducibility when any continuous physiological variable is dichotomised. Agreement between SBPM and ABPM was improved to substantial (systolic BP) or excellent (diastolic BP) when BP was expressed as a continuous variable. The level of agreement as described by ICC does seem slightly at odds with the Bland Altman plot. The random scatter of the plot clearly demonstrated there was no significant bias for any level of systolic BP, which was all it was meant to show. The eye is automatically drawn to seven or eight subjects whose difference in systolic pressure is out-with two standard deviations when measured by both methods. However, the majority (n=62) had a difference in systolic pressure of no more than 10mmHg between both methods. The level of agreement described by the intra-class correlation coefficient was not substantially changed by the few outliers.

This study has also shown that the majority of patients preferred SBPM and that it did not cause any significant anxiety, some specifically commenting that they found it useful to know their blood pressure. The only drawback of SBPM is the absence of information regarding the nocturnal blood pressure. However, until a consensus is reached on treatment of nocturnal pressure, the majority of treating physicians will continue to treat hypertension dependent on daytime blood pressure [McGowan et al 2007].

#### *The superiority of out of office BP measurement*

ABPM is a better predictor of cardiovascular mortality than office BP, irrespective of whether the general population [Sega et al 2005, Kikuya et al 2005], untreated [Perloff

et al 1983, Dolan et al 2006, Staessen et al 1999] or treated [Clement et al 2003] hypertensive population are studied. As such it has generally been accepted as the reference standard for 'out of office' BP measurement. The structured nature of the comparison in the present study arguably explains why we have demonstrated a higher correlation between SBPM and ABPM than in previous studies [Sega et al 1997, Stergiou et al 2000, Gaborieau 2008]. As SBPM is equivalent to ABPM at predicting target organ damage [Stergiou et al 2007, Gaborieau 2008], it could be surmised that differences between ABPM and SBPM are simply due to different measurement strategies, rather than reflecting any real difference in BP.

SBPM has a stronger relationship to cardiovascular risk than OBP in the general population [Ohkubo et al 2004, Mancia et al 2006] and in those with treated hypertension [Bobrie et al 2004]. Both ABPM and SBPM can identify true hypertension, white coat hypertension and masked hypertension (normal office BP and elevated out of office BP). White coat and masked hypertension are common, each affecting 10 -15% of the general population, with the latter associated with a doubling of cardiovascular risk [Ohkubo 2005]. Out of office BP is more reproducible and therefore more likely to represent true BP than OBP [James et al 1988, Warren et al 2008]. Indeed, a recent meta-analysis describing the changes in BP in subjects treated with antihypertensive medication or placebo has demonstrated the improved stability of self-measurements, rather than clinic measurements [Ishikawa et al 2008]. There is also evidence that the use of SBPM can lead to improved compliance with antihypertensive medication [Ogedegbe et al 2006] and improved blood pressure control [Cappuccio 2004, Fahey 2007]. Although ABPM has been shown to be cost-effective in diagnosing hypertension,



it is impractical for assessing and managing all patients in primary care. SBPM is cheaper than ABPM with equivalent diagnostic accuracy and has been proposed by some as the way forward for managing hypertension [Padfield 2002, Parati et al 2008, 2009, Pickering 2008].

Central to the debate on the use of self-monitoring is the question of how many and how often measurements are made. Sole reliance on clinic or office readings may result in miss-classification of patients, either hypertensive or normotensive, in up to 69% of cases [Benediktsson et al 2004]. Ohkubo et al [2004b] have indicated that even one self-measurement in the morning was more predictive of stroke than OBP but the predictive precision improves as the number of readings increases. There remains significant debate on the frequency and mode of operation for SBPM [Stergiou et al 1998,2007, Den Hond et al 2003, Padfield et al 2007, Imai et al 2007].

## ***Conclusion***

I have demonstrated that the current ESH guidelines for self-monitoring are valid when compared directly to ABPM in terms of mean blood pressure and diagnosing both normality and hypertension. Given the vast amount of evidence regarding the superiority of out of office BP measurement, surely self-monitoring of blood pressure is the way forward, as advocated in a recent clinical review? [McManus et al 2008]

## Chapter 8

### ***Summary and Conclusion***

“As a society, we are willing to contemplate widespread genomic or proteomic subject characterization in pursuit of the concept of ‘individualized medicine.’ By contrast, blood pressure measurement is one of the few areas of medical practice where patients in the twenty-first century are assessed almost universally using a methodology developed in the nineteenth. As a consequence, a disconcertingly high proportion of the population may remain at risk for adverse cardiovascular events because their hypertension is neither identified nor treated”. This eloquent statement by Floras (2007) encapsulates the basis of this thesis. Notwithstanding the economic argument, where suboptimal blood pressure control has been estimated to account for 10% of the world’s healthcare expenditure (Gaziano 2009), all physicians are responsible for individual patients and it is our professional responsibility to look after these patients as best we can. The last 10 years have seen the publication of an ever increasing body of evidence documenting the utility of using out of office BP measurement, especially in terms of reproducibility and prognostic significance. It is therefore unacceptable to continue to measure blood pressure as originally described by Korotkov in 1905. Some may argue the evidence base for treating hypertension is solely based on office BP measurement however given the evidence from this thesis and those papers referred to throughout, I think we can safely say the use of office BP measurement is outdated, inaccurate and should be left in the past.

The prime objective in blood pressure measurement is to obtain as true a measure as possible of a patients' mean blood pressure. In diagnosis, this reflects their cardiovascular risk. In blood pressure management, it is essential to know whether or not measured BP truly reflects a change from baseline as a result of intervention, or has this repeat reading simply occurred by chance? There are multiple different factors involved in accurately determining blood pressure which are outlined in the introduction, whether they are patient dependent, observer dependent or dependent on the patient-observer interaction. The reasons that ABPM and SBPM are superior to office measurement are: The use of oscillometric devices removes observer dependent variables such as human error, terminal digit preference, inter-observer variation etc. Out of office measurement removes any variation dependent on patient-observer interaction e.g. white coat hypertension. Therefore, it is only the patient dependent variables which cannot be controlled for with out of office BP measurement. Lastly, it is a statistical fact that as the number of measurements increase, the mean is more likely to represent the true average of a continuous variable such as blood pressure.

The question of how blood pressure is expressed is becoming increasingly discussed. Some proponents suggest that the terms 'hypertensive', 'normotensive' etc should be abandoned. With respect to cardiovascular risk, risk increases in a linear fashion as blood pressure increases and conversely decreases as BP decreases (Lewington 2002). Also, vascular risk is inversely proportional to the degree of nocturnal dipping when expressed as a percentage decline compared to daytime BP, again in a linear fashion (Boggia 2007). Therefore, the process of risk stratification of individual patients is drastically oversimplified by simply describing them as 'hypertensive'. Even if we

remain with the status quo, this assumes patients can be reliably categorized as hypertensive or not. The data presented in chapter 2 demonstrates this dichotomization of a continuous variable is intrinsically flawed. Although the reproducibility of the hypertensive / normotensive dichotomization is marginally better with ABPM rather than office BP (albeit using an oscillometric device), neither is good (kappa values 0.15-0.55). The further subdivisions of white coat and masked hypertension were not examined for reproducibility but dividing 2 categories into 4 will not improve reproducibility.

It therefore seems sensible to regard BP as the true continuous variable that it is and in that way it is more reproducible. The intra-class correlation coefficient is approximately 0.6 for OBP and 0.7-0.8 for ABP measurements. The most important observation is that the ICC values are much more stable over time than the kappa values, signifying this is the most reliable way to examine blood pressure. Chapter 3 addresses the phenomenon of nocturnal dipping in much the same way with the same result – dipping is essentially stable over time if expressed as a continuous variable rather than the traditional ‘dipper / non-dipper’ categorization.

The only other way to improve reproducibility could be to examine repeated episodes of self monitoring as this may improve accuracy of repeated measurements. Myers et al have demonstrated excellent reproducibility of BP expressed as a continuous variable using self monitoring within the office environment (ICC 0.89) but whether this can be replicated or improved upon using self monitoring at home remains to be seen (Myers 2009).

Despite all the evidence and experience of ABPM, there appears to be a lack of knowledge and appreciation of this technology amongst GPs and general physicians. The study in chapter 4 specifically addressed whether or not ABPM diagnosis of hypertension influenced therapeutic aggressiveness. Unfortunately, this study raised more questions than answers! It is well recognised that blood pressure control is suboptimal, with a variety of studies quoting rates of control of 40-50% of the known hypertensive population. Therefore, with an unequivocal diagnosis of hypertension based on ABPM, surely the majority of patients would be treated? It was not clear why only 83% were commenced on treatment and 75% of those started on antihypertensive treatment remained on monotherapy despite sub-optimal office BP. Further qualitative research is needed to answer these questions.

One possible conclusion drawn from the results of chapter 4 is that primary care physicians will still rely more on OBP than ABPM in determining the need for treatment, despite clear evidence of hypertension by the most robust clinical method. As long as this remains the case, patients will continue to be sub-optimally treated. Because of the incentivised climate of the nGMS contract, GPs may prefer to use the blood pressure results obtained within office measurements, taken by those all too aware of the target range, rather than use the more categorical data obtained from ABPM. This in itself is short-sighted. ABPM does result in BP 10/5mmHg lower than OBP and therefore more people would reach the blood pressure targets delineated by the contract if out of office measurements were used more routinely.

Compliance with prescribed medication is a major issue with any long term illness, especially one such as hypertension where there are little symptoms. Chapter 5 clearly demonstrated a persistent reduction in BP, as defined by ABPM, in patients with diabetes attending a pharmacist led blood pressure control service. The minor increase in antihypertensive medication is unlikely to wholly account for the BP reduction. In my opinion, patient education is paramount, especially when delivered by paramedical staff. As a general rule, society still holds the medical profession in very high esteem and therefore rarely asks for explanation or questions us as to the need for medication. Patients are more likely to comply with medication (and as a result have a significant and persistent reduction in BP) if they understand the reasons behind why they take so many tablets. This can be achieved with repeated sessions with a pharmacist or nurse for repetition of education. There is little direct evidence behind this hypothesis (Green 2008) and this opinion is mostly based on clinical experience. It is analogous to the education of patients with type 1 diabetes who undergo the 'DAFNE' education course and have demonstrably improved glycaemic control for many years afterwards.

One improvement in this study would be to assess compliance with medication at the point of referral, during attendance at the clinic and in the follow up period. It is likely that BP reduction is mostly secondary to improved adherence with existing medications, for the reasons described above. Similarly, one of the main comments in the patient questionnaires from chapter 7, regarding SBPM, was their preference for being able to see what their blood pressure was using a home monitor. Perhaps this ability to regularly quantify an asymptomatic disease will enhance adherence to prescribed medications through subjects seeing a "cause and effect". This is analogous to

measurement of blood glucose in diabetes, where more frequent monitoring improves overall glycaemic control.

Although it has been shown to be cost effective in terms of accurate diagnosis resulting in net cost saving due to smaller drug costs, it would be logistically impossible to use ABPM for diagnosis and during the titration phase in all patients. Also, as outlined in chapter 6, there is lack of unanimity amongst hypertension specialists in terms of diagnosis, let alone treatment. In addition, I doubt many patients would be happy to undergo ABPM on a regular basis, such as during the titration phases of antihypertensive medication. Chapter 7 demonstrates the equality of SBPM and ABPM in terms of mean BP measurement and categorization. Also, it confirms patient preference for SBPM. Therefore, could SBPM be the way forward? There are still problems with SBPM, such as lack of a normal range as defined by population studies, patients using only non-validated monitors and monitors requiring a memory function given the problems with reporting accuracy. At present, there are no clinical studies demonstrating reduction in SBPM equates with decreased cardiovascular morbidity and mortality. I would argue that they are not needed. There is overwhelming evidence that reducing blood pressure reduces CVD morbidity and mortality. Self blood pressure monitoring is at least as good as the current gold standard, is far cheaper and preferred by patients.

The basis of this thesis, as set out in the introduction, was to examine ways to improve accuracy and reproducibility of blood pressure measurement. The direct clinical

correlation was to improve patient management, prevent misdiagnosis and define a method for use in everyday clinical practice to adjust antihypertensive medications with the confidence that there has been a true treatment effect rather than a lower BP occurring by chance or regression to the mean.

I hope I have clearly demonstrated the reasons and evidence behind why physicians should no longer check blood pressure within the standard clinical environment and solely use out of office measures to quantify blood pressure. The only real barrier that remains is acceptance of this theory by both patients and physicians.



## **Publications containing work undertaken for this thesis**

1. **McGowan N**, Gough K, Padfield P. "Self blood pressure monitoring: a worthy substitute for ambulatory blood pressure?" *Journal of Human Hypertension* advance online publication 18<sup>th</sup> Feb. 2010
2. **McGowan N**, Atkins N, O'Brien E, Padfield PL. "Computerised reporting improves the clinical use of ambulatory blood pressure monitoring". *Blood pressure monitoring* 2010;15;115-23
3. **McGowan N**, Padfield P. "The long term reproducibility of nocturnal dipping". *Blood Pressure monitoring* 2009;14;185-189
4. **McGowan N**, Strachan MWJ, Cockburn A, McKnight J. "Initial and sustained cardiovascular risk reduction in a pharmacist-led diabetes cardiovascular risk clinic". *British Journal of Diabetes and Vascular Disease* 2008;8:34-38
5. **McGowan N**, Gough K, Maxwell S, Padfield PL. "How do we use Ambulatory measurement of Blood Pressure in the management of Hypertension?" *Blood Pressure Monitoring* 2007;12:385-386

## **Presentations to Learned Societies containing work undertaken for this thesis**

### **British Hypertension Society 2009, Young Investigator Award**

Self Blood Pressure Monitoring: The future of hypertension management.

### **Scottish Society of Physicians 2009**

Self Blood Pressure Monitoring: The new gold standard

### **European Society of Hypertension 2009**

Self Blood Pressure Monitoring: a worthy substitute for Ambulatory Blood Pressure

### **British Hypertension Society 2008**

How do GPs use ambulatory blood pressure monitoring?

### **International Society of Hypertension 2008**

Within-patient variability of blood pressure: Implications for diagnosis and management of hypertension

## Bibliography

Amoore JN, Dewar D, Gough K, Padfield PL. Do Spacelabs ambulatory non-invasive blood pressure recorders measure blood pressure consistently over several years use? *Blood press monit.* 2005;10(1);51-6

Association for the Advancement of Medical Instrumentation. *The national standard of electronic or automated sphygmomanometers*. Arlington, VA: AAMI; 1987

Benediktsson R, Padfield PL. Maximizing the benefit of treatment in mild hypertension: three simple steps to improve diagnostic accuracy. *QJM.* 2004 Jan;97(1):15-20

Ben-Dov IZ, Ben-Arieh L, Mekler J, Bursztyn M. Blood pressure dipping is reproducible in clinical practice. *Blood Press. Monit.* 2005;10;79-84

Bjorklund K, Lind D, Lithell H. Twenty-four hour ambulatory blood pressure in a population of elderly men. *J Intern Med* 2000;248:501-10

Blanco F, Gil P, del Arco C et al. Association of clinic and ambulatory blood pressure with vascular damage in the elderly: the EPICARDIAN study. *Blood Press Monit.* 2006;11;329-335

Bland JM, Altman DG. Statistical methods for assessing agreement between two methods of clinical measurement. *Lancet* 1986;1;307-310

Bland J, Altman D. Measurement error and correlation coefficients. *BMJ* 1996;313;41-42

Bobrie G, Chatellier G, Genes N et al. Cardiovascular prognosis of "masked hypertension" detected by blood pressure self-measurement in the elderly treated hypertensive patients. *JAMA.* 2004;291;1342-49

Boggia J, Li Y, Thijs L. Prognostic accuracy of day versus night ambulatory blood pressure: a cohort study. *Lancet* 2007;370;1219-29

Booth GL, Kapral MK, Fung K, Tu JV. Relation between age and cardiovascular disease in men and women with diabetes compared with non-diabetic people: a population based retrospective cohort study. *Lancet* 2006;368:29-35

Burnier M, Gasser UE. End-digit preference in general practice: a comparison of the conventional auscultatory and electronic oscillometric measurements. *Blood Press* 2008;17;104-109

Cappuccio F, Kerry, S, Forbes L et al. Blood pressure control by home monitoring: a meta-analysis of randomised trials. *BMJ* 2004;329;145-51

Carney S, Gillies A, Garvey L et al. Direct comparison of repeated same-day self and ambulatory blood pressure monitoring. *Nephrology* 2005;10;151-6

Cesar C, Victoria P, Rogelio T. Loaned self-measurement equipment model compared with ambulatory blood pressure monitoring. *Blood Press Monit.* 2003;8;63-70

Chaves H, Menezes Campello de Souza F, Kreiger M. The reproducibility of dipping status: Beyond the cut-off points. *Blood Press Monit* 2005;10;201-205

Chobanian AV, Bakris GL, Black HR et al. National High BP Education Program Coordinating Committee. Seventh Report of The Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High BP. *Hypertension* 2003;42:1206–1252.

Clement D, De Buyzere M, De Bacquer D et al. Prognostic Value of ambulatory blood pressure recordings in patients with treated hypertension. *N Engl J Med* 2003;348;2407-15

Colhoun HM, Betteridge DJ, Durrington PN, Hitman GA, Neil AW, Livingstone SJ, et al. Primary prevention of cardiovascular disease with atorvastatin in type 2 diabetes in the Collaborative Atorvastatin Diabetes Study (CARDS): multicentre randomised placebo-controlled trial. *Lancet* 2004;364:685-96

Conen D, Bamberg F. Non-invasive 24-hr ambulatory blood pressure and cardiovascular disease: a systematic review and meta-analysis. *J Hypertens.* 2008;26;1290-99

Cuspidi C, Meani S, Salerno M, Valerio C, Fusi V, Severgnini B et al. Reproducibility of nocturnal blood pressure fall in early phases of untreated essential hypertension: a prospective observational study. *J Hum Hypertens.* 2004;18;503-509

Cuspidi C, Meani S, Valerio C, Sala C, Fusi V, Masaidi M *et al*. Reproducibility of dipping/non-dipping pattern in untreated essential hypertensive patients: impact of age and sex. *Blood Press Monit*. 2007;12;101-106

Davidson MB, Hix JK, Vidt DG, Brotman DJ. Association of impaired diurnal blood pressure variation with subsequent decline in glomerular filtration rate. *Arch Intern Med*. 2006;166;846-852

Dawes MG, Coats AJ, Juszczak E. Daytime ambulatory blood pressure is better at predicting mortality than clinic blood pressure. *Blood Press Monit* 2006;11:111-8

De la Sierra A, Redon J, Banegas JR *et al*. Prevalence and factors associated with circadian blood pressure patterns in hypertensive patients. *Hypertension*. 2009. Epub

Den Hond E, Staessen J, Celis H *et al* . Antihypertensive treatment based on home or office blood pressure – the THOP trial. *Blood Press Monit*. 2004;9;311-4

Dolan E, Stanton A, Thijs L *et al*. Superiority of ambulatory over clinic blood pressure measurement in predicting mortality. The Dublin Outcome Study. *Hypertension*. 2005;46;156-61

Donnan PT, MacDonald TM, Morris AD. Adherence to prescribed oral hypoglycaemic medication in a population of patients with type 2 diabetes:A retrospective cohort study. *Diabet Med* 2002;19;279-84.

Eliasson B, Cederholm J, Nilsson P, Gudbjonsdottir S. The gap between guidelines and reality: Type 2 diabetes in a national diabetes register 1996-2003. *Diabet Med* 2005;22;1420-26

Fagard R, Staessen J, Thijs L *et al*. Relationship between ambulatory blood pressure and follow-up clinic blood pressure in elderly patients with systolic hypertension. *J Hypertens*. 2004;22;81-87

Fahey T, Schroeder K, Ebrahim S. Interventions used to improve control of blood pressure in patients with hypertension (Review). *The Cochrane Collaboration* 2007

Floras JS. Ambulatory blood pressure: facilitating individualized assessment of cardiovascular risk. *J Hypertens*. 2007;25;1565-8

Gaborieau V, Delarche N, Gosse P. Ambulatory blood pressure monitoring versus self-measurement of blood pressure at home: correlation with target organ damage. *J Hypertens*. 2008;26:1919-1927

Gaziano TA, Bitton A, Anand S *et al*. The global cost of non-optimal blood pressure. *J Hypertens*. 2009;27;1472-7

Graede P, Vedel P, Larsen N, Jensen GVH, *et al*. Multifactorial intervention and cardiovascular disease in patients with type 2 diabetes. *N Engl J Med* 2003;348;343-394

Green B, Cook A, Ralston J *et al*. Effectiveness of Home Blood Pressure Monitoring, Web Communication, and Pharmacist care on Hypertension Control: A randomised controlled trial. *JAMA* 2008;299(24);2857-67

Hales S. Statistical essays containing haemostatics. *Wilson and Nichol, London*. 1769, *Third edition*

Halpern MT, Khan ZM, Schmier JK, Burnier M, Caro JJ, Cramer J, *et al*. Recommendations for evaluating compliance and persistence with hypertension therapy using retrospective data. *Hypertension* 2006;47;1039-48

Hansson L, Zanchetti A, Carruthers SG, Dahlof B, Elmfeldt D, Julius S, *et al*. Effects of intensive blood-pressure lowering and low dose aspirin in patients with hypertension: Principal results of the Hypertension Optimal Treatment (HOT) randomised trial. *Lancet*.1998;351:1755-62

He FJ, MacGregor GA. Cost of poor blood pressure control in the UK: 62,000 unnecessary deaths per year. *J Hum Hypertens*.2003;17:455-7

Head G *et al*. Definition of ambulatory blood pressure targets for diagnosis and treatment of hypertension in relation to clinic blood pressure: prospective cohort study. *BMJ* 2010;340;c1104

Hernandez Del-Rey R, Martin-Baranera M, Sobrino J, Gorostidi M, Vinyoles E, Sierra F *et al*. Reproducibility of the circadian blood pressure pattern in 24-h versus 48-h recordings: the Spanish Ambulatory Blood Pressure Monitoring Registry. *J Hypertens*. 2007;25;2406-2412.

Heskens L, Kroon A, van Oostenbrugge R, Haest R, Lodder J, de Leeuw P. Different classifications of nocturnal blood pressure dipping affect the prevalence of dippers and non dippers and the relation to target organ damage. *J Hypertens*.2008;26:691-8

Hinman AT, Engel BT, Bickford AF. Portable blood pressure recorder. Accuracy and preliminary use in evaluating intradaily variations in pressure. *Am Heart J*.1962: 63;663-8

Holman R, Paul S, Bethel A et al. Long term follow up after tight control of blood pressure in type 2 diabetes. *NEJM* 2008;359(15);1565-76

Holman R, Paul S, Bethel A et al. 10-year follow up of intensive glucose control in type 2 diabetes. *NEJM* 2008: 359(15);1565-76

Hozawa A, Ohkubo T, Kikuya M *et al*. Blood pressure control assessed by home, ambulatory and conventional blood pressure measurements in the Japanese general population: the Ohasama Study. *Hypertens Res* 2002;25;57-63

Huxley R, Barzi F, Woodward M. Excess risk of fatal coronary heart disease associated with diabetes in men and women: meta-analysis of 37 prospective cohort studies. *BMJ* 2006;332:73-8

Imai Y, Aihara A, Ohkubo T et al. Factors affecting blood pressure variability. A community based study in Ohasama, Japan. *Am J Hypertens*. 1997;10;1281-9.

Imai Y, Obara T, Ohkubo T. How many times should we ask subjects to measure blood pressure at home on each occasion? *J Hypertens*. 2007;25(10):1987-91

Ishikawa J, Carroll D, Kuruvilla S, Schwartz JE, Pickering TG. Changes in home versus clinic blood pressure with antihypertensive treatments. *Hypertension*.2008;52:856-864

James GD, Pickering TG, Yee LS *et al*. The reproducibility of average ambulatory, home, and clinic pressures. *Hypertension* 1988;11;545-9

Janeway TC. The clinical study of blood pressure. New York and London: D Appleton and Co.1904

Jula A, Puukka P, Karanko H. Multiple clinic and home blood pressure measurements versus ambulatory blood pressure monitoring. *Hypertension* 1999;34;261-6



- Julius S et al. Outcomes in hypertensive patients at high cardiovascular risk treated with regimens based on valsartan or amlodipine: the VALUE randomised trial. *Lancet* 2004;363:2022-29.
- Kikuya M, Ohkubo T, Asayama K et al. Ambulatory blood pressure and 10-year risk of cardiovascular and non-cardiovascular mortality: the Ohasama study. *Hypertension* 2005;45;240-245
- Kikuya M, Hansen T, Thijs L et al. Diagnostic thresholds for ambulatory blood pressure monitoring based on 10-year cardiovascular risk. *Circulation* 2007;115;2145-52
- Krakoff L. Cost-effectiveness of ambulatory blood pressure. A Reanalysis. *Hypertension* 2006;47;29-34.
- Levy D, Garrison R, Savage D et al. Prognostic implications of echocardiographically determined left ventricular mass in the Framingham Heart Study. *N Engl J Med* 1990;323;1706-7
- Lewington S, Clarke R, Qizilbash N et al. Prospective studies collaboration. Age-specific relevance of usual blood pressure to vascular mortality: a meta-analysis of individual data for one million adults in 61 prospective studies. *Lancet* 2002;360;1903-13
- Lorgelly P, Siatis I, Brooks A et al. Is ambulatory blood pressure monitoring cost-effective in the routine surveillance of treated hypertensive patients in primary care? *Br J Gen Pract.* 2003;53;794-6
- Lowey A, Moore S, Norris C, Wright D, Silcock J, Hammond P. The cost effectiveness of pharmacist-led treatment of cardiac risk in type 2 diabetes. *Pharm World Sci* 2007 March 30 – EPUB ahead of print.
- Little P, Barnett J, Barnsley L et al. Comparison of agreement between different measures of blood pressure in primary care and daytime ambulatory blood pressure. *BMJ* 2002;325;254-60
- Mancia G, Sega R, Bravi C et al. Ambulatory blood pressure normality: results from the PAMELA study. *J Hypertens* 1995;13;1377-90
- Mancia G, Zanchetti A, Agabiti-Rosei E et al. Ambulatory blood pressure is superior to clinic blood pressure in predicting treatment induced regression of left ventricular hypertrophy. *Circulation* 1997;95;1464-70



Mancia G, Facchetti R, Bombelli M et al. Long term risk of mortality associated with selective and combined elevation in office, home, and ambulatory blood pressure. *Hypertension*. 2006;47;846-853

Mancia G et al. 2007 ESH-ESC Practice guidelines for the Management of Arterial Hypertension. *J Hypertension* 2007;25:1751-1762.

Manning G, Rushton L, Donnelly R, Miller-Craig MW. Variability of diurnal changes in ambulatory blood pressure and nocturnal dipping status in untreated hypertensive and normotensive subjects. *Am J Hypertens*. 2000;13;1035-1038

McGowan N, Gough K, Maxwell S, Padfield P. How do we use ambulatory blood pressure in the management of hypertension? *Blood Press. Monit.* 2007;12;385-6

McGrath BP. Ambulatory blood pressure monitoring. *Med J Aus* 2002;176:588-592.

McManus RJ, Ryan A, Greenfield S, Pattison HM, Clifford S, Marriott J, Wilson S. Self measurement of blood pressure: a community survey. *J Hum.Hypertens*. 2007;21:741-743.

McManus RJ, Glasziou P, Hayen A, Mant J, Padfield P, Potter J et al. Blood pressure self monitoring: questions and answers from a national conference. *BMJ* 2008;337:a2732

Medical Research Working Party. MRC trial of treatment of mild hypertension: principle results. *BMJ* 1985;291;97-104

Mengden T, Medina R, Beltran B. Reliability of reporting self-measured blood pressure values by hypertensive patients. *Am J Hypertens* 1998;11;1413-7

Mochizuki Y, Okutani M, Donfeng Y, Iwasaki H, Takusagawa M, Kohno I et al. Limited reproducibility of circadian variation in blood pressure dippers and non dippers. *Am J Hypertens*. 1998 :11(4); 403-9.

MRC/BHF Heart Protection Study of cholesterol lowering with simvastatin in 5963 people with diabetes: a randomised placebo-controlled trial. *Lancet* 2003;361;2005-16

- Myers M, Valdivieso M, Kiss A. Consistent relationship between automated office blood pressure recorded in different settings. *Blood Press Monit.* 2009;14;108-111
- Niiranen T, Kantola I, Vesalainen R et al. A comparison of home measurement and ambulatory monitoring of blood pressure in the adjustment of antihypertensive treatment. *Am J Hypertens* 2006;19;468-74
- O'Brien E, Sheridan J, O'Malley K. Dippers and non-dippers (letter). *Lancet* 1988;2;397
- O'Brien E, Petrie J, Littler WA, de Swiet M, Padfield PL, Altman D *et al.* The British Hypertension Society Protocol for the evaluation of automated and semi-automated blood pressure measuring devices with special reference to ambulatory systems. *J Hypertens.* 1990;8;607-619
- O'Brien E, Mee F, Atkins N, O'Malley K. Accuracy of the Spacelabs 90207 determined by the British Hypertension Society protocol. *J Hypertens.* 1991;9;573-574
- O'Brien E, Coats A, Owens P *et al.* Use and interpretation of ambulatory blood pressure monitoring: recommendations of the British Hypertension Society. *BMJ* 2000;320;1128-34
- O'Brien E, Pickering T, Asmar R et al. Working group on blood pressure monitoring of the European Society of Hypertension International Protocol for validation of blood pressure measuring devices. *Blood Press Monit.* 2002;7;3-17
- O'Brien E, Asmar R, Beilin L *et al.* European Society of Hypertension Working Group on Blood Pressure Monitoring. European Society of Hypertension recommendations for conventional, ambulatory and home blood pressure measurement. *J Hypertens* 2003;21:821-48
- O'Brien E, Asmar R, Beilin L *et al.* Practice guidelines of the European Society of Hypertension for clinic, ambulatory and self blood pressure measurement. *J Hypertens.* 2005;23;697-701
- O'Brien E. Ambulatory blood pressure measurement. The case for implementation in primary care. *Hypertension.* 2008;51;1435-41
- Ogedegbe G, Schoenthaler A. A systematic review of the effects of home blood pressure monitoring on medication adherence. *J Clin Hypertens (Greenwich).* 2006 (8);174-180

Ohkubo T, Hozawa A, Yamaguchi J, Kikuya M, Omhoni M, Michimata M *et al.* Prognostic significance of the nocturnal decline in blood pressure in individuals with and without high 24-h blood pressure: The Ohasama study. *J Hypertens* 2002;20:2183-2189

Ohkubo T, Asayama K, Kikuya M *et al.* Prediction of ischaemic and haemorrhagic stroke by self-measured blood pressure at home: the Ohasama study. *Blood Press Monit.* 2004;9;315-20(a)

Ohkubo T, Asayama K, Kikuya M *et al.* How many times should blood pressure be measured at home for better prediction of stroke risk? Ten year follow up results from the Ohasama study. *J Hypertens.* 2004;22;1099-1104(b)

Ohkubo T, Kikuya M, Metoki H *et al.* Prognosis of "masked" hypertension and "white coat" hypertension detected by 24-h ambulatory blood pressure monitoring. 10 year follow up from the Ohasama Study. *J Am Coll Cardiol* 2005;46;508-15

Omboni S, Parati G, Palatini P, Vanasia A, Muiesan ML, Cuspidi C *et al.* Reproducibility and clinical value of nocturnal hypotension: prospective evidence from the SAMPLE study. *J Hypertens.* 1998;16;733-738

Owens P, Atkins N, O'Brien E. Diagnosis of white coat hypertension by ambulatory blood pressure monitoring. *Hypertension.* 1999;34:267-272

Padfield PL. Self-monitored blood pressure: a role in clinical practice? *Blood press monit.* 2002;7(1);41-4

Padfield P & Parati G Home blood pressure monitoring in clinical practice: how many measurements and when? *Journal of Hypertension.* 2007, 25(7):1337-1339

Palatini P, Mormino P, Canali C, Santonastaso M, De Venuto G, Zanata G *et al.* Factors affecting ambulatory blood pressure reproducibility. Results of the HARVEST trial. *Hypertension.* 1994;23:211-216

Palmas W, Pickering T, Teresi J *et al.* Ambulatory blood pressure monitoring and all cause mortality in elderly people with diabetes mellitus. *Hypertension.* 2009;53;120-7

Parati G, Staessen JA. Day-night blood pressure variations: mechanisms, reproducibility and clinical relevance. *J Hypertens.* 2007;25;2377-2380

Parati G, Stergiou GS, Asmar R *et al.* European Society of Hypertension guidelines for blood pressure monitoring at home: a summary report of the second international consensus conference on home blood pressure monitoring. *J Hypertens* 2008;26;1505-30

Parati G, Omboni S, Bilo G. Why is out-of-office blood pressure measurement needed?: Home blood pressure measurements will increasingly replace ambulatory blood pressure monitoring in diagnosis and management of hypertension. *Hypertension* 2009;54;181-7

Parati G, Pickering TG. Home blood pressure monitoring: US and European consensus. *Lancet* 2009;373;876-878

Perloff D, Sokolow M, Cowan R. The prognostic value of ambulatory blood pressures. *JAMA* 1983;249;2792-98

Pickering TG, James GD, Boddie C *et al.* How common is white coat hypertension? *JAMA* 1988;259;225-8

Pickering T. Recommendations for the use of home (self) and ambulatory blood pressure monitoring. *Am. J. Hypertens.* 1995;9;1-11

Pickering T. American Society of Hypertension ad-hoc panel. Recommendations for the use of home (self) and ambulatory blood pressure monitoring. *Am J Hypertens.* 1996;9;1-11

Pickering TG, Hall JE, Appel LJ *et al.* Recommendations for Blood Pressure Measurement in Humans and Experimental Animals. *Circulation* 2005;111;697-716

Pickering TG, Shimbo D, Haas D. Ambulatory Blood Pressure Monitoring. *NEJM* 2006;354;2368-74

Pickering T, Miller NH, Ogedegbe G *et al.* Call to action on use and reimbursement for home blood pressure monitoring. *Hypertension* 2008;52

Quality and outcomes framework – Hypertension. April 2004-March 2005.  
[www.isdscotland.org/qof](http://www.isdscotland.org/qof)

Rasmussen SL, Torp-Pederson C, Borch-Johnson K, Ibsen H. Normal values for ambulatory blood pressure and differences between casual blood pressure and

ambulatory blood pressure: results from a Danish population study. *J Hypertens* 1998;16:1415-24

Rahmana M, Griffina V, Heykac R, Hoita B. Diurnal variation of blood pressure: Reproducibility and association with left ventricular hypertrophy in haemodialysis patients. *Blood Press Monit* 2005; 10;25-32

Richards C, Sutherland M, Gough K, Padfield P. Direct access ambulatory blood pressure monitoring-the Edinburgh Experience. *Blood Press Monit.* 2004;9(6):287-291

Richardson DW, Honour AJ, Fenton GW, Stott FD, Pickering GW. Variations in arterial blood pressure throughout the day and night. *Clin Sci.* 1964; 26; 445-460.

Rogers M, Small D, Buchan D et al. Home monitoring service improves mean arterial pressure in patients with essential hypertension. *Ann Intern Med.* 2001;134;1024-32

Sala C, Santin E, Rescaldani M et al. How long shall the patient rest before clinic blood pressure measurement? *Am J Hypertens.* 2006;19;713-7

Sayk F, Becker C, Teckentrup C et al. To dip or not to dip: on the physiology of blood pressure decrease during nocturnal sleep in healthy humans. *Hypertension.* 2007;49;1070-6

Schettini C, Bianchi M, Nieto F, Sandoya E, Senra H. Ambulatory blood pressure: normality and comparison with other measurements. Hypertension working group. *Hypertension* 1999;34;818-25

Scottish Health Survey 2003:vol 1;chapter 9.  
<http://www.scotland.gov.uk/Resource/Doc/76169/0019731.pdf>

Sega R, Cesana G, Milesi C et al. Ambulatory and home blood pressure normality in the elderly: data from the PAMELA population. *Hypertension* 1997;30;1-6

Sega R, Trocino G, Lanzarotti A. Alteration of cardiac structure in patients with isolated office, ambulatory or home hypertension. Data from the general population (Pressioni Arteriose Monitorate e Loro Associazioni (PAMELA) study). *Circulation* 2001;104;1385-92

Sega R, Facchetti R, Bombelli M et al. Prognostic value of ambulatory and home blood pressures compared with office blood pressure in the general population. Follow up

results from the Pressioni Arteriose Monitorate e Loro Associazioni (PAMELA) study. *Circulation* 2005;111;1777-83

Shimbo D, Kuruvilla S, Haas D *et al.* Preventing misdiagnosis of ambulatory hypertension: algorithm using office and home blood pressures. *J Hypertens.* 2009;27;1775-83

Sixth National report of the Joint National Committee on prevention detection, evaluation, and treatment of high blood pressure. *Archives Int Med.*1997;157:2413-2446

Staessen J, Byttebier G, Buntinx F *et al.* Antihypertensive treatment based on conventional or ambulatory blood pressure measurement: a randomized controlled trial. *JAMA* 1997;278;1065-72

Staessen JA, Bieniaszewski L, O'Brien E, Gosse P, Hayashi H, Imai Y *et al.* Nocturnal blood pressure fall on ambulatory monitoring in a large international database. *Hypertension* 1997;29(1-pt1);30-39

Staessen J, Thijs L, Fagard R *et al.* Predicting cardiovascular risk using conventional vs ambulatory blood pressure in older patients with systolic hypertension. *JAMA* 1999;282;539-46

Stanton A, Cox J, Atkins N *et al.* Cumulative sums in quantifying circadian blood pressure patterns. *Hypertension* 1992; 19;93-101

Stergiou G, Skeva I, Zourbaki A, Mourtoulakis T. Self-monitoring of blood pressure at home: how many measurements are needed? *J Hypertens.* 1998;16:725-731

Stergiou G, Skeva I, Baibas N *et al.* Diagnosis of hypertension using home or ambulatory blood pressure monitoring: comparison with the conventional strategy based on repeated clinic blood pressure measurements. *J Hypertens* 2000;18;1745-51

Stergiou G, Salgami E, Tzamouranis *et al.* Masked hypertension assessed by ambulatory blood pressure versus home blood pressure monitoring: Is it the same phenomenon? *Am J Hypertens.* 2005;18;772-8.

Stergiou GS, Giovas PP, Gkinos CP, Patouras JD. Validation of the Microlife WatchBP home device for self home blood pressure measurement according to the international protocol. *Blood Press Monit.* 2007.12;185-188



Stergiou G, Argyraki K, Moysakis I. *et al.* Home blood pressure is as reliable as ambulatory blood pressure in predicting target-organ damage in hypertension. *Am J Hypertens.* 2007;20;616-21

Stergiou G, Baibas N, Kalogeropoulos P. Cardiovascular risk prediction based on home blood pressure measurement: the Didima study. *J Hypertens.* 2007;25:1590-1596

Stergiou GS, Parati G. The optimal schedule for self-monitoring of blood pressure by patients at home. *J Hypertens.* 2007;25;1992-1997

Stergiou GS, Tzamouranis D, Nasothimiou ES *et al.* Are there really any differences between home and daytime ambulatory blood pressure? Comparison using a dual mode ambulatory and home monitor. *J Hum Hypertens.* 2009 July 16 [epub ahead of print]

Stewart MJ, Brown H, Padfield PL. Can simultaneous ambulatory blood pressure and activity monitoring improve the definition of blood pressure? *Am J Hypertens.* 1993 Jun;6(6 Pt 2):174S-178S

The 2006 Gallup study of the hypertension market. Princeton,NJ:Multi-sponsor surveys inc;2006

The National Institute for Health and Clinical Excellence. Clinical guideline 34. Management of hypertension in adults in primary care: partial update. Costing report. June 2006. [www.nice.org.uk](http://www.nice.org.uk)

Turner R, Holman R, Stratton I, Cull C, Frighi V, Manley S, *et al.* Tight blood pressure control and risk of macrovascular and microvascular complications in type 2 diabetes:UKPDS 38. *BMJ* 1998;317:703-712

Verberk W, Kroon A, Kessels A *et al.* Home blood pressure measurement: a systematic review. *J Am Coll Cardiol.* 2005;46;743-51

Verdecchia P, Schillaci G, Guerrieri M, Gatteschi C, Benemio G, Boldrini F, Porcellati C. Circadian blood pressure changes and left ventricular hypertrophy in essential hypertension. *Circulation.* 1990;81;528-536.

Verdecchia P, Porcellati C, Schillaci G, Borgioni C, Ciucci A, Batistelli M *et al.* Ambulatory blood pressure. An independent predictor of prognosis in essential hypertension. *Hypertension* 1994;24;793-801

Verdeccia P, Angeli F, Mazzotta G, Gentile G, Reboldi G. Home blood pressure measurements will not replace 24-hour ambulatory blood pressure monitoring. *Hypertension* 2009;54;188-95

Warren RE, McGowan NJ, Padfield PL. Within-patient variability of blood pressure: Implications for diagnosis and management of hypertension presented at the 22nd Scientific Meeting of the International Society of Hypertension, held in Berlin, Germany, from June 14 to 19, 2008

Williams B, Poulter NR, Brown MJ *et al.* British Hypertension Society. Guidelines for management of Hypertension: report of the fourth working party of the British Hypertension Society, 2004 BHS-IV. *J Hum Hypertens.* 2004;18:139-85

Williams B, Lindholm LH, Sever P. Systolic pressure is all that matters. *Lancet* 2008;371;2219-21

World Health Organization-International Society of Hypertension guidelines for the management of hypertension. *J Hypertens* 1999; 17:151-183

Zakopoulos NA, Nanas SN, Lekakis JP *et al.* Reproducibility of ambulatory blood pressure measurements in essential hypertension. *Blood Press.Monit.* 2001;6;41-45